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Studies in Maternal Deprivation in Infants' Homes

by GUNNAR KLACKENBERG

The results of Spitz's investigations, which were published in the forties, are of the greatest interest not only to pediatricians, child psychologists and nursery personnel, but also to some psychiatrists and psychologists in different parts of the world, who have been persistently stimulated to test and retest the old notions in the light of his findings: that the inadequate relationship of an infant with his mother even during the first year of his life may, in an unfavourable environment, lead to irreversible defects in endowment and to profound changes in personality.

Since Bowlby, a few years ago, made Spitz's investigations more generally known through his WHO report, and applied them in a wider context, it is no longer possible to dismiss them as improbable and fantastic. It seems quite clear to me that Spitz's careful documentation of the problem in the different annual volumes of the *Psychoanalytical Study of the Child* affords a much sounder basis for judging the findings of his investigations than do his films which deal with the same subject. For although these films achieved considerable publicity, their conclusiveness has been seriously questioned. They may serve a useful purpose by stimulating experts, but only by exercising discrimination and making reservations can they be shown to the unfortunate mothers and fathers who have been compelled to leave their children in an infants' home. Conditions in Sweden are very different from those depicted in the films. This applies at least to those infants' homes in Stockholm where the present investigation was conducted.

The purpose of this investigation is to answer the question: What are the actual conditions in infants' homes in Stockholm? To what extent can the emotional and mental changes in the infants, which are attributable to separation from the mother, be determined by the methods employed? Can a friendly atmosphere to children really counteract such serious defects as those which are described by Spitz? Is there any difference between the emotional reactions and the mental development of the infants who

were institutionalized from the very outset, and those who were taken care of in an infants' home only after they had been in close relationship with their mothers for six months?

The Sample

The sample consisted of infants from eight infants' homes with a total capacity of 179. These homes are either run or supervised by the Stockholm Board of Social Welfare of Children. About 400–500 infants are admitted annually. Some of the infants stay only a short time in the homes, while others remain there until they are one year of age; in many cases they are then taken to foster homes or return to their parents' homes. When they are one year of age, a small number of the infants are transferred, for various social reasons, to other children's homes. Consequently a large number of the infants grow up and develop, even during their first year of life, without having a continuous relationship with their mothers. In most cases, the reasons for institutionalization are: the mother's illness, the housing shortage, a desire to have the infant adopted, or the general disorganized condition of the home.

One of the groups investigated consisted of infants who had been taken care of from the time they were less than one month of age up to approximately one year of age (Group 1). The other group comprised infants who had been taken care of in an institution only after they were six months of age, and who, prior to this, had been continually cared for by their own mothers (Group 2). A large number of these infants came from mothers' hostels. The mothers had stopped breast-feeding their infants, and wanted to start working, in the more or less vain hope that subsequently, when their situation improved, they would again be able to look after their children. The second group was investigated after they had been at least three months in an infants' home.

There is no difference in social origin between the two groups. The infants came from different social strata, and percentually, the lowest levels naturally predominated. Selection was not influenced by any considerations of heredity. In the first place, all infants who fulfilled the above-mentioned conditions as to their period of institutionalization, have been regularly reported for investigation. In order to obtain as homogeneous a sample as possible and one that could also be readily estimated, we subsequently introduced certain restrictions of a medical nature. Every baby had to weigh more than 2500 g at birth and be free from any trace or suspicion of cerebral injury, whether sustained in connection with delivery or at a later period, and furthermore, it must not have had any serious illness. Mild infections, such as pharyngobronchitis and mild forms of diarrhoea, naturally had to be tolerated so as to obtain a sample at all. Any infant who suffered from definite heart disease or exhibited any bodily malformation, mongolism, etc., was excluded. Any infants in Group 1 who had to suspend their stay in the children's home in order to receive hospital treatment, and any in Group 2 who were, for the same reason, separated from their mothers for some time before their admission to the children's home, were also excluded from the sample, as this suspension caused an interruption in the kind of care. Thus the only difference between the two groups was the length of time they were looked after in the children's home, and that the infants in Group 2 had had a continuous relationship with their mothers during the first six months of life. The investigation was discontinued when both groups comprised 50 infants.

The control group consisted of foster children who, from the first month of life right up to one year of age, had been looked after in their prospective adoptive homes. The same criteria, concerning their state of health, were applied as those for the other groups. From the point of view of origin, this was the most homogeneous group that it was possible to use. This group, like the other groups referred to, contained children born out of wedlock and some born in wedlock. Owing to the kindness of the superviser of the foster home, it was possible to investigate all the children who, according to her records for a given period, fulfilled the above conditions. Not a single family refused to collaborate. In view of the strict conditions imposed in respect of the period of care and of its continuity, it is only natural that considerable time was required to obtain this sample. Consequently, Group 3 is composed of only 21 children.

Methods of Investigation

The children were subjected to a Bühler-Hetzer test, examined physically and observed at play. For Groups 1 and 3 the investigations were always conducted at a time which was as near as possible to the day when the children were one year of age. The infants comprising Group 2 were also usually investigated at this age, but as the criterion for this group was, that the infant had been separated from his mother for at least three months when he was between six and twelve months of age, this implied that some of the infants were investigated when they were between nine and twelve months of age. During the investigations all the children were observed in the environment and in the room to which they were accustomed. As regards the foster children, this was similar to a home visit by the investigators. Nothing out of the ordinary occurred and no special arrangements were made. Even the Bühler-Hetzer tests, which were carried out by a trained psychologist,[1] were fitted in as naturally as possible and were only administered when the child felt thoroughly rested. What was relatively unfamiliar in the situation, was the same for all the children, and consisted of the test materials, the experimenter, and the author. In some cases it proved necessary to allow the nurse or the foster mother to have the child on her knee in order to be able to make the observations and to carry out the tests, because of the child's fear, which he had such difficulty in overcoming.

Some of the infants in Group 2 were subjected to observation not only when they had been three months in the children's home but also immediately after admission. It would have been of value, if this dual observation could have been carried out for all the children, so as to note the changes in behaviour and in the degree of development. But in order to obtain 50 children for this group, we should have had to investigate practically all the infants between six and nine months of age who had been newly admitted to the children's homes, since it was impossible for us, in advance, to have either estimated or influenced the actual length of stay in the children's home. But with our small working team this was quite out of the question. In 14 cases, however, we were right in our supposition that the children would remain in the home longer than three months.

We used the Bühler-Hetzer test on the one hand, because until quite recently this was the test method for infants usually employed in Sweden, and consequently we felt most conversant with this test, and, on the other hand, because Spitz himself had

[1] I wish to express my gratitude to Mrs. Hanna-Greta Odhner for her valuable assistance.

used it in his investigations. In this way, the results can be more easily compared. It should be pointed out at once, however, that this method is not standardized for any sample of Swedish children. The numerical values of the developmental quotients, which are given below, should not be judged on the same basis as that used for the standardized Terman-Merill intelligence quotient. It is not the magnitude of the mean values of the quotients for the groups, which is in itself of the greatest interest for this investigation, but rather the interrelations of these values. The children's behaviour during the tests and the other observations, their way of making relationships with other people, and of handling toys, their fearlessness or anxiety, all these factors are equally important in enabling us to form a picture of their reactions, even if they cannot be assigned numerical values. When testing infants, emotional factors undoubtedly play a relatively more important role than they do when testing older children. As a prognosis of the child's future development, the Bühler-Hetzer quotient is regarded as having only a restricted value.

Results

It proved quite impossible to test 4 of the infants in Group 1 on account of their anxiety and negativism, in spite of the fact that two attempts were made on consecutive days. For the reactions of these infants who were unwilling to be tested, see below. The mean quotient for the remaining 46 children in this group was 108 ± 1.449. The marginal values of the quotients were 87 and 131.

It was impossible to obtain reliable quotients for 6 of the infants in Group 2. The arithmetic mean of the quotients for the remaining 44 infants was 105 ± 1.760. The limit values were 81 and 124.

All the children in Group 3 (foster children) evinced interest and took part in the systematic developmental tests, their reactions being positive almost without exception. The mean of the quotients for these 21 children was 120 ± 2.793. The limit values were 91 and 140.

The difference in quotients between Group 3 and Group 1 is 12; and as this is three times greater than the standard error ± 3.146 ($= 9.438$), it is statistically significant. The same applies with regard to the differences in quotients between Group 3 and Group 2. On the other hand, there is no appreciable difference between the two groups whose length of stay in the infants' home differed.

Among the 14 infants in Group 2, who were tested immediately after admission and again after at least three months' residence in the infants' home, 4 refused to take part in the second series of tests; all the infants participated in the first series. The mean quotients for the remaining 10 children fell from 115 to 108 during their residence in the home.

The emotional reactions of the infants to the test materials, and to the experimenter or the observer, also differed between the groups. As has been

mentioned above, not less than 10 of the 100 infants from the infants' homes exhibited such pronounced negative reactions that they could not be tested, whereas the foster children made contacts, without any particular difficulties, with the unfamilar visitor and the toys he used for testing. All emotional grades were represented in the two groups from the infants' homes. These ranged from shyness and reserve during the first few minutes, to a period of manifest diffidence, which lasted for a remarkably long time, and culminated in excessive anxiety and desperation, which resulted in a refusal to be tested. The most striking reactions were displayed by the group of infants (Group 2) who were reared by their mothers during the first period of their lives and were subsequently separated from them for at least three months. In the test or play situations, approximately half of these infants behaved in a way which differed from that normally found in an infant of the same age. While one-third of the children who had spent a long time in an infants' home (Group 1) reacted in a similar manner. Practically the entire group of foster children manifested quite a different sense of security. The short reactions of shyness, which were normal for this age, soon gave way to spontaneous curiosity and a craving for action, which the test material usually stimulates. Only in one case, did we feel justified, in the light of the same criteria as those applied in the case of the infants from the infants' homes, in designating the deviation as remarkable; inasmuch as the girl adopted a temporizing attitude to our advances for a surprisingly long time, and further contact also proved unstable. The tests were carried out, however, without any appreciable difficulty.

The critical changes in personality, termed by Spitz "anaclitic depression", which were found to exist in a highly developed state in not less than 10 out of 123 cases in his sample, were seldom met with in our sample. According to Spitz, the syndrome of the disease develops in infants aged between six and twelve months, who had previously had a good relationship with their mothers which they now lacked. Consequently, in the present study, we should expect to find these children especially in Group 2. After some months of maternal deprivation in an infants' home, these infants, who had formerly been happy, extroverted, and desirous of making contacts, now became, according to Spitz, peevish, discontented, anxious and irritable. After some time, this condition gives rise to a serious incapacity to make relationships with people, which is especially dangerous in view of its effect on the subsequent development of personality. The children become introverted, are oblivious of their environment, and take no interest in the efforts of their nurses to amuse them. They have a serious, melancholy expression and appear to be inwardly frigid; they do not give much trouble, and once they have passed through the peevish phase they are looked upon

as good children. But their good behaviour is not the outcome of their joy in living; there is no babbling or sputtering; they have no initiative and make no contacts. In its severe form, they appear to be suffering from depression, anaclitic depression, which results in their becoming incapable of making relationships with other people. They have lost the bond—the emotional contact—without which it is not possible to rear them. The symptoms of this disease should not be confused with the reactions which take place immediately after admission to an infants' home. The latter form of depression is, as a rule, of a more occasional and transitory nature. According to Spitz, infants, who have suffered from anaclitic depression for longer than three months, have sustained irreparable damage. If the mother-child relationship is re-established at an earlier period, apparently the symptoms may disappear completely.

This condition has never been described by any observer in Sweden. This may be due either to its rarity or to the fact that sufficient attention has not been paid to this phenomenon. These infants appear to be mentally backward, and may often be considered to be backward owing to hereditary or other causes which are unknown. But even if an investigation specially aims at detecting the fully developed syndrome in a group of infants systematically examined, as in the present study, the results obtained are not convincing. The following is the only case which may possibly fulfil the requisite conditions.

Girl aged $11^1/_2$ months, institutionalized since 6 months of age; prior to this, stayed with her mother, first in a mothers' hostel and then in a family where the mother was working as a domestic help. Development normal; was happy and alert, showed an interest in her environment before her stay in the infants' home. On admission was not appreciably different from the other infants. The changes in her condition took place during the latter months prior to investigation, when she became more withdrawn, and was liable to sit absent-mindedly on the chamber or in bed, smiling to herself for no apparent reason. She only chuckled when she was tickled.

During the investigation she was preoccupied, rocked the upper part of her body slightly, paid only superficial attention to the experimenter, held her head on one side and stared at the lamp hanging from the ceiling. Her sense of hearing seemed to be impaired. (The auditory examination at the outpatient department for ear diseases at the Karolinska Sjukhuset showed that she could perceive sounds.) She displayed neither fear nor joy when she was investigated, and was oblivious of her environment. When the nurse tried to attract the infant's attention by lifting her up and talking to her, this only proved successful for a short time; she was not interested, and whenever she looked at anything this was apparently quite by chance. Somatically she was normal. The mother, who is employed by the National Telephone System, is gentle and attentive, her cheerful exterior conceals an underlying sadness. She is interested in the girl, visited her and planned to take her home as soon as accommodation could be arranged. The girl's Bühler-Hetzer developmental quotient was 91; during the test she was absent-minded, engrossed in herself, and made no contacts. Serious and at-

tentive when playing bo-peep, but not to the extent that this could be termed a positive reaction. Sat and rocked herself; showed no displeasure when a toy was taken from her.

Arrangements were made to take her home sooner. A little more than a year later she was under observation in a nursery school, where she displayed similar deviations in her behaviour and a tendency to isolate herself. Compliant, in a passive, uninterested way. Her Bühler-Hetzer developmental quotient was then 83. Hearing normal.

The change in the girl's behaviour, resulting in autistic tendencies, coincided with her separation from her mother. Among all the possible causes, in view of her anamnesis, this is the only one which has a direct bearing on the mental deviations observed.

Consequently, in this case, only the possibility existed of the presence of the fully developed syndrome. The emotional instability displayed in many of the reactions of the institutionalized infants (particularly those belonging to Group 2), which was referred to above, may perhaps be regarded as the initial symptoms of the disease caused by deprivation, which, when fully developed, exhibit the tragic characteristics of anaclitic depression. The difference in the mental climate, which is due to the fact that the infants' homes investigated by us were better staffed than those investigated by Spitz, is possibly the prerequisite condition for a more efficient prophylaxis. This will be considered more fully below.

Discussion

Although the investigation shows that there is a difference between institutionalized infants and foster children in respect to both their degree of development and their emotional disturbances, nevertheless the results of care in Stockholm infants' homes are very different from those described by Spitz. The latter's findings should be regarded as a background. He compared infants from an infants' home, where they had been placed for social reasons (such as the mother's illness, etc.), with infants from a combined infants' home and mothers' hostel, to which the mothers, on account of their asocial behaviour, had been committed for a long period (it was attached to a prison). In the latter case, the mothers looked after their children with only a small staff to supervise them. These children were looked upon as handicapped by their heredity, but with regard to the special circumstances under which the mothers were living, the children proved a great stimulation to them and afforded an outlet for their pent-up affections. The infants in both groups were subjected to regular, systematic Bühler-Hetzer tests until they were one year of age. The mean quotients, which were the same at the start, fell for the group from the infants home (61 infants) from 105 to 72, while the quotient for the group of infants living in the prison remained normal.

It is not difficult to find a plausible explanation for the fact that the results of the investigation of the infants from the Stockholm infants' homes were so much more positive when compared with those for the infants' homes described by Spitz. The latter also had a high standard of hygiene and were in daily contact with a well-trained pediatrician; furthermore, their diet was satisfactory and the premises were adequate from the point of view of preventing infection. But they lacked the one point which, in this respect, is perhaps most essential: a sufficiently large personnel—nurses and mother-substitutes. Each nurse (in this category, every member of the personnel is included who was in direct contact with the children) had about 7–8 children to take care of. This implies that there was hardly enough time for even the routine physical care, and no time at all for intercourse with the children over and above looking after them.

When our investigation was conducted, each nurse (except for kitchen staff, we count the whole personnel as nurses) at the Stockholm infants' homes had 2–3 children to look after. Under these circumstances nurses have more time at their disposal and do not need to stifle their inherent desire to play with and fondle the children; they need not be afraid of picking them up and having them around them on the floor or of letting them sit on their knee. As a rule, the homes try to arrange that the same nurse is responsible for "her" children throughout their stay in the home. The work is not regarded merely as a duty, but affords emotional pleasure to the mutual advantage of both parties. But this fostering care does require time, and one of the preconditions is that personnel may be readily recruited. Despite the progress made during recent decades with regard to the social care of children, there is still room for further improvement in this field.

We pediatricians and child psychiatrists must regard it as one of our essential tasks, in respect to our work with infants' homes, to arrange that mother-substitutes have ample time to make emotional relationships with the children. Prugh *et al.*, working with a sample of pre-school children, have recently succeeded in showing, with the aid of well-selected control groups, that hospitalization reactions may be reduced to a certain extent by the mental atmosphere that surrounds the children when in hospital. Continuity of care should also be recommended here.

It may be assumed that the differences, as found in the present study, between the infants from the infants' homes and the foster children, are due to the fact that the latter represent a better selection from the point of view of heredity. There is not much that can be said in support of this; but only a discretionary estimate has been made of the data contained in the records of the Board of Social Welfare of Children. In fact, it would prob-

TABLE 1

Group 1 (11–12 months' care in infants' homes).

No.	Sex	Age in mos.		Reasons for placing infants in the homes	Previous residence	Bühler-Hetzer	Reactions during investigation
		On admission	When investigated				
1	M	1¼	12	Married, bad housing conditions	1 month at home	103	No comment
2	M	<1	11½	Unmarried mother, wants to board out child for adoption	Maternity hosp.	123	,, ,,
3	M	<1	11¾	Married, in hospital (puerperal psychosis)	,,	Impossible to test (2 attempts)	Anxious, yelled. Reticent in presence of investigator
4	M	<1	11¼	Married, in hospital (puerperal psychosis)	,,	100	Serious, contact no comment
5	F	<1	11	Unmarried, epileptic mother, unable to nurse child	,,	105	No comment
6	F	<1	11½	Incest child	,,	87	Serious, impaired contact not anxious
7	M	<1	11¾	Unmarried, homeless mother	Maternity hosp. + few weeks in foster home	109	No comment
8	M	<1	11	Unmarried mother	Maternity hosp.	110	No comment
9	M	<1	12	Unmarried mother, suffering from t.b.	,,	106	,, ,,
10	F	<1	12	Married, housing shortage	,,	100	Anxious, neurotic
11	M	<1	12	Married, suffering from t.b.	,,	115	No comment
12	M	<1	11½	Unmarried mother, nervous, not interested in child	,,	106	,, ,,
13	M	<1	12¼	Married, both parents suffering from t.b.	,,	102	Sensitive to sound, anxious and cautious with new toys; twitchings.
14	M	<1	11¼	Married. Mother wants to board out child for adoption; has two children already, bad financial position	,,	114	No comment
15	M	1½	12¼	Unmarried, homeless mother	,,	118	,, ,,
16	M	<1	11¾	Unmarried mother, wants to board out child for adoption	,,	113	,, ,,
17	M	<1	12¼	Incest child	Maternity hosp.	Impossible to test	Screamed, irritable
18	M	<1	11¼	Unmarried mother; puerperal eclampsia	,,	Impossible to test	Pronounced anxiety reaction
19	M	<1	11½	Unmarried mother, wants to board out child for adoption	,,	126	No comment
20	F	<1	11¼	Unmarried mother, wants to board out child for adoption	,,	120	,, ,,
21	F	<1	12	Married. Father, though suffering from t.b., insists living at home	,,	116	Moderate reaction of shyness
22	F	<1	12	Unmarried mother, wants to board out child for adoption	,,	112	No comment. Phlegmatic
23	M	<1	11¼	Unmarried mother, does not want to see her child	,,	126	No comment
24	F	<1	12½	Unmarried mother, suffering from t.b., wishes to board out child for adoption	,,	105	Temporary but pronounced reaction of shyness
25	M	<1	12½	Unmarried mother, wants to board out child for adoption	,,	118	No comment
26	F	<1	11½	Unmarried mother, mentally ill	Just back from maternity hosp.	114	,, ,,
27	M	<1	11	Unmarried mother. Homeless, domestic help	Maternity hosp. + Norrtull Children's Hosp.	131	,, ,,
28	M	<1	11¾	Unmarried mother. Unfit to look after child	Maternity hosp.	102	Intense reaction, peevish, irritable, paralysed at times, passive towards toys
29	M	<1	12	Unmarried mother, in mental hospital. Infant to be adopted	,, ,,	95	Temporary reaction of shyness, but rather submissive, not very gay
30	M	<1	11¼	Mother married, but husband not father to the child. Homeless, not interested in the child	Maternity hosp. + short time at home	99	Anxious. First test unsuccessful. Dull impression
31	F	1¼	12	Married mother; serious puerperal depression	Maternity hosp. + short time at home	121	No comment
32	M	<1	11¼	Unmarried mother, wishes to board out child for adoption	Maternity hosp.	106	Practically no comment. Temporary reaction of shyness
33	M	<1	11	Unmarried mother, wants to board out child for adoption; no interest, moreover suffering from t.b.	,, ,,	104	Apathetic, quite absent-minded, "institutionalized child", poor contact
34	F	<1	11½	Mother unmarried, suffering from t.b.; will subsequently take child home and get married	,, ,,	91	Poor contact detached, isolated. Spasmus nutans
35	F	<1	11½	Parents married. Father suffers from t.b.; mother supervised by t.b. dispensary	,, ,,	101	Temporary reaction of shyness, no comment
36	F	<1	11¼	Parents married. Mother ill; soon after died of cancer	Maternity hosp. + at home short time	96	No comment. Quite submissive during tests
37	M	<1	12¼	Parents married; homeless; houseboat unsuitable for child	Maternity hosp.	116	No comment
38	M	<1	11¼	Unmarried mother, acc. med. cert. may not take care of child (nervous disease)	,, ,,	100	No comment. Slightly insecure when investigated but not during tests
39	M	<1	12½	Unmarried mother, insane	,, ,,	109	No comment
40	M	<1	11¾	Mother unmarried; nervous trouble; dwelling unsuitable	,, ,,	95	Reserved, difficult to test because of his paralysed condition. Retested next day. Moderate reaction during investigation
41	F	<1	11¾	Mother unmarried, wished to board out child for adoption, but changed her mind after one year	,, ,,	99	Phlegmatic. Contact not impaired, indolent
42	M	<1	12	Mother unmarried, mentally depressed, frail	,, ,,	Impossible to test, 2 attempts	Very anxious and labile, impaired social contact
43	M	<1	11¼	Mother married, homeless	,, ,,	122	No comment
44	F	<1	12	Mother unmarried, "social development retarded", overcrowded	,, ,,	97	Reserved at outset, somewhat tense
45	F	<1½	12	Mother unmarried, housing shortage	Maternity hosp. + own home short time	105	At first very pronounced reaction of shyness, improved later, but never got over her anxiety
46	F	<1	11½	Parents married, housing shortage	Maternity hosp.	104	Temporary reaction of shyness, probably also continued to be a little reserved
47	F	<1	12	Parents married, mother delicate, tired; discord in home	,, ,,	111	No comment
48	M	<1	12	Mother unmarried, homeless	,, ,,	113	,, ,,
49	M	1½	12	Housing shortage; mother divorced, acc. med. cert. incapable of working	Own home short time	111	No comment. Normal reaction of shyness
50	M	1½	12	Same (Twin to No. 49)	,, ,,	113	No comment

Table 2

Group 2 (3–5 months' care in infants' homes).

No.	Sex	Age in mos.		Reasons for placing infants in the homes	Previous residence	Bühler-Hetzer (1. on admission 2. on discharge)	Reactions during investigation
		On admission	When investigated				
1	M	6½	11½	Mother unmarried, homeless	Mothers' hostel	122	Labile, no comment
2	F	7	11	Mother unmarried, has to work	,, ,,	1) 117 2) Impossible to test	1) No comment 2) Very anxious
3	F	7¼	11¾	Mother unmarried, suffers from tuberculous pleurisy	Own home	114	No comment
4	M	6½	11½	Mother unmarried, homeless	Mothers' hostel	103	Shy of strangers, screamed
5	M	7½	10½	Mother a widow; works at night	Own home	123	No comment
6	M	6½	11½	Mother unmarried, homeless	Mothers' hostel	110	,, ,,
7	F	6¼	10¾	Mother unmarried, homeless, has to work	,, ,,	1) 107 2) 99	1) No comment 2) Insecure reaction to strangers
8	M	8	11½	Married, lives in condemned house	Own home	88	Anxious, insecure, sensitive, pronounced emotional disturbance
9	M	6¾	11¼	Mother unmarried, in sanatorium, suffering from t.b.	Parents' home	100	Restless, insecure reaction to strangers
10	F	7¾	12	Mother unmarried, homeless	Mothers' hostel	82	Sensitive, easily irritated. Not without contacts but these unstable
11	F	8½	12	Both parents in sanatorium, suffer from t.b.	Own home	1) 120 2) 121	1) Temporary reaction of shyness 2) Anxious, but only temporarily
12	F	7	11½	Under protection of Local Authority, to prevent risk of neglect	Own home	106	Superficial contact, tense, neither anxious nor cheerful
13	F	6	9	Mother unmarried, homeless	Mothers' hostel	103	No comment
14	M	8½	11¼	Parents married. Mother ill	Own home	1) 108 2) 110	Insecure, labile reaction to strangers
15	F	7½	12	Married, homeless	,, ,,	113	Reserved, moderately anxious during investigation, labile
16	M	8½	12¼	Married; separated, mother ill	Own home	Impossible to test	Seriously disturbed, anxious, on her guard, impossible to carry out test
17	F	6	10	Mother unmarried, homeless	"Own home"	1) 98 2) Impossible to test	1) No comment 2) Impossible to test, afraid of test-material
18	M	6½	10¾	Married, homeless	Mothers' hostel	98	No comment
19	F	6	10½	Mother unmarried, homeless	,, ,,	122	,, ,,
20	F	8½	11¾	Married, mother suffering from t.b.		110	,, ,,
21	F	5½	10½	Unmarried mother, young schoolgirl	Own home Mothers' hostel	97	Serious, astonished, a little anxious and cautious
22	M	6¼	10½	Mother unmarried, homeless	,, ,,	106	No comment
23	M	8½	11¼	Married, homeless	"Own home"	110	Labile, sensitive to frustration
24	F	6½	11¼	Mother unmarried, homeless	Mothers' hostel	90	Phlegmatic, mutely uninterested, but not without contacts
25	M	9¼	12½	Unmarried mother	,, ,,	112	No comment
26	M	9	12	Married, homeless, mother in mental observation ward	"Own home"	1) 119 2) 108	Somewhat reserved, but not commented upon
27	M	8	11½	Mother unmarried, homeless	Mothers' hostel	100	Reserved to begin with, thoroughly paralysed, later reasonable
28	F	6½	11½	Mother unmarried, homeless	Mothers' hostel	116	No comment
29	M	7½	10¾	Married, supervision by Local Authority as father an alcoholic	Own home	119 (min. val)	Intense and protracted reaction of shyness
30	M	6	10½	Mother unmarried, homeless	"Own home"	107	No comment
31	F	7½	12	Mother unmarried, homeless	Mothers' hostel	124	,, ,,
32	M	6	11½	Mother unmarried, feeble-minded psychopath, homeless	,, ,,	80	Dull, no comment
33	M	6	11	Mother unmarried, homeless	,, ,,	100	No comment
34	M	6½	11¼	Mother unmarried, homeless, in domestic service	"Own home"	107	Shy of strangers, abnormal reaction
35	F	7	12	Married, homeless	,, ,,	109	Quite strong reaction even after an hour's observation
36	F	8¾	11¾	Mother unmarried, furnished room, cannot have child. Domestic service too strenuous for her	Mothers' hostel	1) 132 2) 112	1) Quiet, sensitive, tried make contact; interested in the testing 2) Shy at first. Quite indiff. to testing, less active
37	M	8¼	10¼	Mother unmarried, homeless	,, ,,	81	No comment
38	F	7¼	11¼	Mother unmarried, homeless, in domestic service	,, ,,	101	Labile. Good during tests, anxious during investigation
39	F	6¼	10¼	Mother unmarried, maid	,, ,,	1) 104 2) 100	No comment
40	F	6	12	Mother unmarried	,, ,,	104 (min. val.)	Shy, difficult to test, anxious at intervals
41	M	6	12	Same	,, ,,	116	No comment
42	F	9	12	Parents married, mother suffering from thyreotoxicosis, operated	Own home	1) 134 2) 108	1) Good contact 2) Artificial contact
43	F	7½	10½	Parents married, divorcing. Mother neurotic. Father an alcoholic	,, ,,	86	Suppressed, serious. Otherwise no comment. Lacks energy
44	F	6	11¼	Mother unmarried, domestic servant, dispensary inspection; later married father of child	Mothers' hostel + dwelling where maid	91	Absent-minded, poor contact, serious
45	M	6	10¾	Mother unmarried, starting to work, homeless	Mothers' hostel	1) 107 2) 119	1) No comment 2) A bit shy, otherwise no comment
46	F	9	12½	Mother unmarried, in mental hosp.	"Own home" with different relatives	1) 129 2) Impossible to test	1) No comment, positive 2) Noticeably disturbed
47	F	9	11¾	Parents married, mother ill, operated	Own home	Impossible to test, 2 attempts	Pronounced anxiety
48	M	6	10½	Parents married, mother cannot manage boy, husband suffering from t.b.; 4 other children	,, ,,	118	No comment
49	M	9	12	Parents married, homeless	"Own home"	1) 95 2) 92	Quiet, a little apathetic and dull, divertible interest.
50	M	7¾	11¾	Parents married, homeless	"Own home"	1) 144 2) Impossible to test satisfactorily	1) No comment 2) Very anxious and irritated

TABLE 3

(Group 3 (11–12 months' care in foster homes).

TABLE 3

Group 3 (11–12 months' care in foster homes).

No.	Sex	Age in mos.		Reasons for foster care	Previous residence	Bühler-Hetzer	Reactions during investigation
		On admission	When investigated				
1	F	¼	12¼	Unmarried mother	Maternity hosp.	139	No comment
2	M	1¾	14½	,, ,,	Mothers' hostel	118	,, ,,
3	F	¼	11	,, ,,	Maternity hosp.	112	,, ,,
4	M	¼	13	,, ,,	,, ,,	132	No comment, a little cautious however
5	M	¼	14½	Parents married. Adoptive mother boy's paternal aunt	,, ,,	91	No comment
6	M	¾	14¾	Mother unmarried, 4th child out of wedlock, looks after the others	Maternity hosp. + asylum	96	No comment, but quotient uncertain owing to lack of concentration
7	F	¼	13¾	Mother unmarried	Maternity hosp.	113	No comment
8	F	¾	12½	Mother unmarried, young parents	,, ,,	107	,, ,,
9	M	1	14	Mother unmarried	Mothers' hostel	132	,, ,,
10	F	¼	12½	,, ,,	Maternity hosp.	132	,, ,,
11	M	½	12¾	,, ,,	,, ,,	115	No comment, sensitive
12	M	1¾	13¾	,, ,,	Mothers' hostel	118	No comment
13	M	¼	11¼	Mother unmarried, sibling of adoptive father	Maternity hosp.	140	,, ,,
14	M	1	15½	Parents married, several children	,, ,,	109	,, ,,
15	M	¾	13	Mother unmarried	,, ,,	126	,, ,,
16	M	¼	11½	,, ,,	,, ,,	130	,, ,,
17	F	2	13¾	,, ,,	Maternity hosp. + infants' home	116	,, ,,
18	M	<1	11¾ ½	,, ,,	Maternity hosp. + children's hosp.	117	Temporary reaction of shyness
19	M	<1	11¾	,, ,,	Maternity hosp.	123	Vital, cheerful, easily contacted, no comment
20	M	2	13½	,, ,,	Maternity hosp. + mothers hostel	116	Quiet, cheerful, harmonious, no comment
21	M	1½	11¾	,, ,,	Maternity hosp. + asylum	135	Cheerful at once, desired contact. No comment

ably be impossible to obtain reliable information about the fathers, some of whom were unknown. We were unable to find any control group which was more appropriate for purposes of comparison than the one used here.

After studying these investigations and findings, we feel disposed to make some comments of a more practical character. The great importance of the part played by the mother-substitute has already been stressed. She can at most, however, be only a mitigating factor. In its wider significance, prevention is here, as elsewhere, of far-reaching importance. Even if it should appear unlikely that we can hope, within a reasonable space of time, to be able to prevent a large number of children from being deprived, even in infancy, of their relationship with their biological mothers, it should be possible to arrange for this separation to take place at a time which is better suited to the emotional and mental needs of the children. It is probably preferable to institutionalize an infant during the first six months of his life rather than between the age of six and twelve months. Mothers should not be compelled to stay in the mothers' hostels if it is evident that they will not be able to look after their infants subsequently. In this connection, breast-feeding is of minor importance when compared with the interruption of the incipient relationship with the mother and of the initial development of the *ego*. For the child's sake, adoption should take place at an early stage, in any case, before he is six months of age. If the observations, necessary for controlling development during infancy, are postponed at the institution, this may cause, under adverse circumstances, inhibition of development. We should endeavour to arrange the definitive placement of infants as early as possible, and to avoid their transfer from infants' homes to homes for small children, even if they are a little more than one year of age. If children who have become thoroughly accustomed to an infants' home after staying there for a year, are transferred in this way, they may react just as unfavourably as children, who have to leave their families, do on admission to an institution. The emotional and mental growth of an infant, who is often transferred at this age, may be compared with the growth of a plant, which runs the risk of withering, if its roots are continually being pulled up. In the light of our knowledge of these facts, we pediatricians must not shirk our responsibility to assist the social-service authorities in their work.

Summary

The developmental and emotional reactions of a group of infants who, up to one year of age, were continuously taken care of in foster homes, have been compared with (1) infants who, also up to one year of age, were looked after in infants' homes, and (2) another group of infants who, only after they were six months of age, were

separated from their biological mothers, and were taken care of in infants' homes for a period of at least three months. The difference between the foster children and the infants from the infants' homes was statistically significant. This difference is by no means as great, however, as that reported for instance by Spitz. Emotional stability was lowest in the infants who, after being together with their mothers for some time, were subsequently deprived of this relationship. No definite case of the critical personality change, which is known as anaclitic depression, was detected among the institutionalized infants. In general, the emotional and mental atmosphere in the infants' homes was very good, and the average number of infants per nurse was a maximum of three.

Etude de l'effet de la privation maternelle dans des homes pour nourrissons.

On a comparé les réactions de l'émotivité et du développément d'un groupe de nourrissons, qui avaient été soignés jusqu'à l'age d'un an par des mères nourricières avec 1) des nourrissons qui ont été soignés également jusqu'à l'âge d'un an dans des pouponnières et 2) un autre groupe de nourrissons, qui ont été séparés de leur mère biologique seulement après avoir atteint l'âge de six mois et ont été soignés alors dans des pouponnières pendant une période d'au moins trois mois. La différence entre les enfants placés en nourrice et les nourrissons de pouponnière était statistiquement significative. Cette différence n'est en aucun cas aussi grande que celle rapportée par exemple par Spitz. La stabilité de l'émotivité était la plus basse chez les nourrissons, qui après avoir été en contact avec leur mère pendant un certain temps, en étaient par la suite privés. On n'a trouvé aucun cas déterminé de changement critique de la personnalité, connu sous le nom de « dépression anaclitique », parmi les nourrissons ayant vécu dans un institut. L'atmosphère émotive et mentale était en général très bonne dans les pouponnières et le nombre moyen de nourrissons par infirmière ne dépassait pas trois.

Studien über Mütterentzug in Säuglingsheimen.

Die entwicklungsmässigen und emotionellen Reaktionen einer Gruppe von Säuglingen, die bis zum ersten Lebensjahr fortlaufend von privaten Pflegemüttern (Pflegekinder) betreut wurden, sind verglichen worden mit 1) Säuglingen, die, ebenfalls bis zum ersten Lebensjahr, in Kinderheimen versorgt wurden und 2) einer anderen Gruppe von Säuglingen, die, als die erst sechs Monate alt waren, von ihren natürlichen Müttern getrennt und für eine Zeit von mindestens drei Monaten in Säuglingsheimen untergebracht wurden. Der Unterschied zwischen den Pflegekindern und den Heimkindern war statistisch bemerkenswert. Dieser Unterschied ist jedoch keineswegs so gross, wie es z. B. von Spitz berichtet wird. Die emotionelle Stabilität war bei den Säuglingen am geringsten, die, nachdem sie einige Zeit mit ihren Müttern zusammen gewesen waren, dieser Beziehung allmählich beraubt wurden. Kein deutlicher Fall von kritischer Persönlichkeitsveränderung, bekannt als anaklitische Depression, wurde unter den Heimkindern entdeckt. Im allgemeinen war die emotionelle und geistige Atmosphäre in den Säuglingsheimen sehr gut und die Durchschnittszahl der Kinder pro Schwester betrug im Höchstfall drei.

El efecto del alejamiento de la madre en niños aislados.

Se estudió el desarrollo y las reacciones emocionales de un grupo de niños que hasta la edad de un año fueron cuidados en casas de familia comparándolo con: 1) niños

que también hasta la edad de un año fueron vigilados en "infant homes"; 2) otros que recién a los seis meses de edad fueron separados de sus madres biológicas y cuidados en "infant homes" por períodos no menores de tres meses. La diferencia entre los niños cuidados en casas de familia y los de "infant homes" fué de significación estadística aunque esta diferencia no fué tan grande como la comunicada por SPITZ por ejemplo. La estabilidad y la emotividad fué mas baja en los niños que después de haber estado en contacto con sus madres durante un cierto tiempo, fueron separados de ellas. No se encontró, en ningún caso, cambios críticos de la personalidad conocidos como "anaclitic depression" entre los niños que vivieron en instituciones. En general, la atmósfera emocional y mental en los casos provenientes de "infant homes" fué muy buena no pasando de tres el número de lactantes por enfermera.

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Blood Gas Determinations on Premature Infants

I. Investigations of Premature Infants without Respiratory Complications

by WILHELM BLYSTAD

An extensive literature has grown up concerning the respiratory complications of the premature infant. In spite of this, the number of well-established facts is still relatively small.

Through blood gas determinations the author has made an attempt to clarify the respiratory situation in a number of premature infants. The study includes examination of 9 infants without any respiratory difficulties and of 12 infants who were in serious respiratory distress.

This publication is the first of a series of three. Here, the laboratory methods are described, and the results obtained on premature infants without any respiratory complications are reported.

Earlier investigations indicate that premature infants, in cases without neonatal complications, probably do not suffer from severe respiratory insufficiency. The arterial oxygen saturation seems to differ very little from normal values for adults (GRAHAM and co-workers, JONXIS). The acid-base conditions in a large number of premature infants have been investigated by REARDON and co-workers. The average CO_2 tension in this material was 38 mm Hg, which does not differ much from that of normal adults. The results showed a relatively wide spread, however, and in 10 per cent of the cases a respiratory acidosis was present.

This study on normal prematures represents a re-investigation of the problem, in which a somewhat different laboratory method has been employed. It is, besides, a necessary basis for evaluating the displacements in the values which are seen in premature infants suffering from severe respiratory complications.

Laboratory Methods

Cutaneous blood obtained by heel puncture, 0.22 ml in volume, was employed in the analyses. Determinations of the CO_2 tensions were made by using a modification of the method described by RILEY and co-workers. Part of the same blood sample was transferred to a centrifuge tube, for subsequent centrifuging and determination of the plasma CO_2 content. In this case a modification of the method described by ROUGHTON and SCHOLANDER was employed. From the values for CO_2 tension and plasma CO_2 content thus obtained, blood pH values were read on Van Slyke's nomogram (PETERS and VAN SLYKE 1931).

Sampling.—A temporary cover was constructed for the Armstrong incubator in order to make it possible to carry out the sampling without discontinuing oxygen administration (Fig. 1). This cover shelters about half of the opening of the incubator, and from its free end the plastic material continues as a curtain to the bottom of the incubator. The infant can remain in the incubator, in a sort of tent, and there is sufficient space for his leg to be brought out into the uncovered part for the sampling. The plastic cover can be put into place by slightly opening the cover of the incubator.

The infant should be left as quiet as possible until the heel puncture can be carried out. In this study the first two drops of blood following the puncture were dried away. The blood was then collected with a pipette without delay, in order to avoid the formation of large drops and to prevent smearing of the blood. As soon as the desired blood volume, about 0.22 ml was obtained, the sample was transferred to a Roughton-Scholander (R-S) syringe.

Determination of the CO_2 and O_2 tensions.—These determinations were carried out by equilibrating the blood with a small gas bubble and analyzing the gases in an R-S syringe. The dead space of the syringe had previously been filled with mercury, and a small amount of heparin-fluoride mixture had been drawn in. The fluoride content gave a concentration in the sample of about 0.10 per cent. When the blood sample was being introduced the last 10 per cent was left in the capillary of the syringe. This part of the sample, together with most of the mercury, was then removed. Only a little of the mercury was left in the capillary as a gas lock for the sample.

The gas mixture employed in the equilibration was kept in a metal container in compressed form. The composition has been: 5.8 per cent CO_2, 9.2 per cent O_2, and 85 per cent N_2. The mixture was transferred to the syringe by a rubber bladder, connected to a pipette. The ratio of the volume of the gas bubble to that of the sample was 1 : 15.4. After the introduction of the small gas bubble the sample was again sealed with mercury. Fig. 1 shows the situation in the syringe at the beginning of the equilibration.

The R-S syringe was then placed in a water bath of 38°C for 8 minutes' rotation, after which a part of the sample, 0.12–0.15 ml was transferred to a small centrifuge tube by means of a pipette. The operation of the introduction of the sample was here reversed. The blood was collected under mineral oil and chilled for subsequent determination of the CO_2 content in plasma.

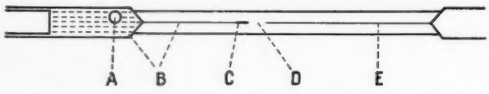

Fig. 1. The situation in the Roughton-Scholander syringe at the onset of the equilibration. *A*, gas bubble; *B*, blood sample; *C*, mercury lock; *D*, air; *E*, physiologic NaCl solution.

Determination of the composition of the gas bubble was then carried out by measuring the volume of the bubble before and after the absorption of the contents of CO_2 and O_2 respectively. A solution of 4 per cent NaOH was employed for the absorption of CO_2. A pyrogallol solution was employed for the O_2 absorption.

The partial pressure of the gasses was computed on the basis of their percentage concentration in the bubble and the atmospheric pressure.

For this method, it is necessary that the gas tensions of the blood should not change significantly during the equilibration. The quantity of blood should be large in proportion to the volume of the bubble, and the difference between the tensions should be small at the outset of the equilibration. In the present determinations the blood sample was small, and the latter's ratio to the volume of the gas bubble was consequently relatively small, i.e. 15.4 : 1.

Changes in the CO_2 tension of the blood caused by uptake of small amounts of CO_2 can be computed by means of the dissociation curve of the blood for CO_2 (CHRISTIANSEN and co-workers). A change in the CO_2 tension of the bubble of 7 mm Hg during the equilibration will give a change in the tension of the blood of a little less than 0.2 mm Hg. For instance, if the tension in the blood is as high as 80 mm Hg, the analysis should give an inaccuracy of about 1 mm Hg.

The CO_2 tension of the blood will also be affected by changes in the O_2 content caused by the equilibration. The dissociation curve for CO_2 is dependent on the O_2 saturation of the blood. The actual changes in the CO_2 tension would, however, be very slight here. Furthermore, in patients suffering from a respiratory insufficiency an increase of the CO_2 tension will mostly occur in connection with a decrease of the O_2 tension. The two factors will thus tend to compensate each other.

The changes in the CO_2 tension caused by the equilibration should therefore be slight, and should only to a small extent influence the results. This was confirmed by a comparison between the results obtained by equilibration and the indirectly determined CO_2 tension. In the indirect method the blood pH was determined with a pH meter, and Van Slyke's apparatus was employed for the analysis of the plasma CO_2 content. Readings of the CO_2 tension have then been made from Van Slyke's nomogram.

The results for the O_2 tension will, however, be far from accurate when the O_2 tension is high. The volume of the bubble will be too large in proportion to the quantity of blood. Even a very slight exchange of gas between the bubble and the blood will here cause considerable alterations in the tension of the blood. When the O_2 saturation comes down to about 90 per cent slight changes will, however, no longer greatly affect the O_2 tension. Thus when the tension of the blood is about or below the tension of the bubble, 65.4 mm Hg, the O_2 analyses should give reliable results. Accordingly, the method should be suitable for studying conditions of hypoxemia.

Material

The investigations were carried out on 9 premature infants with an average birth weight of 1450 g. In the course of the first days of life frequent analyses were carried out. Later the intervals between them were longer. Eighty-eight analyses were performed in all, in the course of the first 10 weeks of life. The clinical data are summarized as follows:—

Table 1

Complications of pregnancy and birth in 9 premature infants who had no neonatal respiratory complications.

	Complications of pregnancy	Birth complications	Initiation of respiration
Case 2	Severe toxemia	Induction	—
Case 4	Toxemia	—	—
Case 9	Ante partum hemorrhage	—	—
Case 10	—	—	—
Case 12	Toxemia	Premature rupture of the membranes	—
Case 13	Mild toxemia	Triplet Breech	—
Case 17	—	Twin Extraction	—
Case 20	—	Twin	—
Case 21	—	Twin Extraction	Transient cyanosis

1. The birth weight ranged from 1130–1730 g, with an average of 1450 g. Three of the patients were twins, one was a triplet.

2. The facts regarding the pregnancy and the delivery are shown in Table 1.

3. Significant respiratory complications were not present in any of the cases.

4. There was no evidence indicating cerebral injury, vitium cordis, or other grave organic disease, except retrolental fibroplasia, which occurred in three of the cases.

5. The colour was satisfactory with the usual O_2 administration. The respiration seemed unaffected, though somewhat shallow at times, and in all the cases it was more or less irregular.

6. During the first days of life a physical examination of the lungs showed transient fine rales, especially on deep inspirations. However, no marked physical changes were noted.

7. In five of the premature infants there occurred in the course of the study moderate symptoms of an upper respiratory infection, but the breathing remained unaffected. One of the patients appeared to be somewhat weaker, whereas the general condition of the others seemed unchanged. In one of these patients X-ray examination of the thorax revealed small central densities which were assumed to be atelectases.

8. All the infants received incubator treatment. Oxygen was administered during a fairly long period, varying from 14–27 days. Most of the time the oxygen administration was 3 liters per minute, with a subsequent gradual reduction until the O_2 administration was discontinued.

Five of the premature infants were given mother's milk, with the addition of an amino acid preparation. Four of the infants were given cow's milk formulae. The first

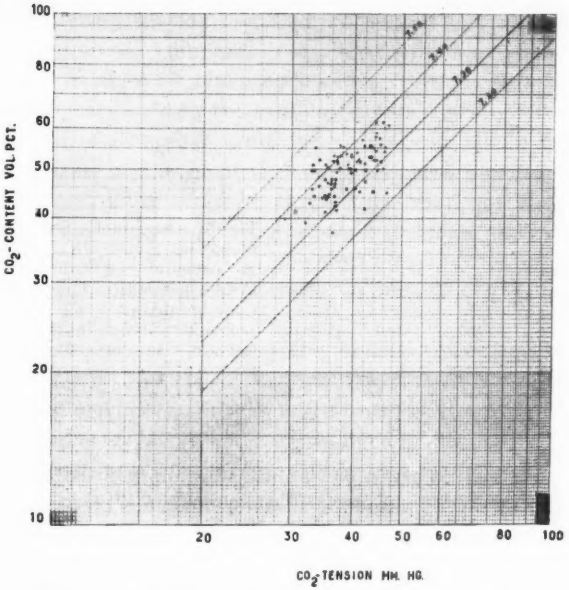

Fig. 2. CO_2 tension, plasma CO_2 content and pH of cutaneous blood in premature infants who had no neonatal respiratory complications. The samples are taken at intervals in the course of the first ten weeks of life.

6 weeks they received equal parts of milk and water, with 7 per cent sugar; later, 2 parts of milk and 1 part of water, with 5 per cent sugar. Vitamins were added in all cases.

9. All the patients survived, and the general condition seemed satisfactory on discharge from hospital.

Results

The results for the CO_2 tensions, CO_2 content and pH's are plotted on a Peters and Van Slyke logarithmic graph (Fig. 2). The average CO_2 tension for the entire material was 39.2 mm Hg. The individual results showed a relatively wide spread, ranging from 28.9–46.3 mm Hg. The average for the CO_2 content in plasma was 50.5 volumes per cent. Here, too, the spread was quite wide, ranging from 37.8–62.3 volumes per cent. The average for the blood pH was 7.36, the individual results ranging from 7.24–7.49.

The values for the CO_2 content in plasma for prematures given cow's milk and prematures given mother's milk have been compared, the values obtained from the beginning of the second week of life to the fifth week of life serving as a basis for the comparison. The average for 20 determinations

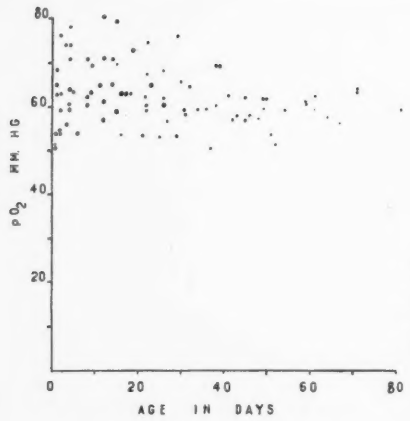

Fig. 3. Oxygen tensions of cutaneous blood in premature infants who had no neonatal respiratory complications. Circles indicate samples obtained under O_2 administration (30–40 per cent O_2). Dots indicate samples taken while breathing air. Results above 65 mm Hg are inaccurate, i.e. too low.

on 4 premature infants given cow's milk was found to be 50.3 volumes per cent. The corresponding value for 19 determinations on 5 prematures given mother's milk was 51.6 volumes per cent; thus no difference was found between the two groups.

Discontinuation of the O_2 administration did not seem to affect the CO_2 content in plasma. Determination of the last two samples taken prior to the discontinuation for all the premature infants gave an average of 49.6 volumes per cent. The corresponding value for the first two samples taken after the discontinuation was 52.4 volumes per cent.

The results of the O_2 determinations are plotted in Fig. 3. Most of the samples from the first 20 days of life have been obtained during O_2 administration. These results show a relatively wide spread. About one third of the values are higher than the tension of the bubble, 65.4 mm Hg, while two thirds of the results show values ranging from 50–65 mm Hg. After the first 20 days of life the vast majority of the samples were obtained during respiration in a normal atmosphere. In these instances most of the values are lower than the tension in the bubble, between 50 and 65 mm Hg. The limitations of the method and the interpretation of the results will be discussed later.

Comments

The Laboratory Methods

It is probably impossible to obtain blood samples from small infants under standard respiratory conditions as the puncture will lead to some crying and restlessness. For this reason the samples cannot be regarded as directly representative of the respiratory situation before the sampling;

they will reflect this situation modified by the changes brought about by the sampling. To obtain comparable results it will therefore be important to reduce these changes as much as possible; further, this factor should vary as little as possible from one sampling to another.

The procedure of sampling which was employed allows the infant to remain undisturbed in the incubator until the heel puncture was made, after which the sampling could be carried out relatively easily, avoiding any delay or complications. There is no need to break off the oxygen administration, and the conditions do not alter greatly from time to time. It would be very difficult to obtain arterial or venous blood samples under similar, advantageous conditions.

Several methods for anaerobic sampling of cutaneous blood have been described (HYTTEN and CHERRY, PETERS and VAN SLYKE 1932). However, none of these was employed in the present investigations. The author's experience was that a much better blood flow was obtained if the blood was allowed to flow freely, without application of any object to the skin. This was found necessary in order to obtain regularly satisfactory cutaneous samples from the small premature infants. The loss of CO_2 caused by the sampling and by the further handling of the blood sample was determined. The results showed that the fall was relatively moderate, and indicated a correction factor corresponding to 1.025 for the CO_2 tensions, and 1.027 for the plasma CO_2 contents.

Earlier investigations have shown that the 0_2 saturation of cutaneous blood does not differ much from that of arterial blood (LUNDSGAARD and MØLLER, LILLIENTHAL and co-workers, HULTGREN and HACKETT). Some investigators have employed local application of heat to increase the arterialisation of cutaneous blood. This has not been the case in the present investigations, as it was feared that such a procedure might cause changes in the acid-base balance.

The changes in the blood gas tensions caused by the equilibration have been discussed above. The changes in the CO_2 tensions will be slight, and only to a small extent affect the results of the analysis. The results of the O_2 analyses will be inaccurate when the O_2 tensions and the O_2 saturations are high. However, when the results are lower than the tension of the bubble, i.e. 65 mm Hg, the values obtained should be reliable; accordingly the method should be applicable for studying conditions of hypoxemia.

CO_2 Analyses and pH

The average CO_2 tension of cutaneous blood in premature infants was found to lie at about the same level as that of arterial blood in adults. The

results agree well with those of REARDON and co-workers mentioned above. Judged from these average values there should be no deficiency in the CO_2 elimination of premature infants in cases without respiratory complications.

The individual values for the CO_2 tensions showed a relatively wide spread, however. This spread may be a product of changes in the respiratory situation caused by the sampling. It is also possible that spontaneous changes in the respiration are of importance here. Variations in the respiratory rate, rhythm, and volume are characteristic of premature infants (SMITH).

In agreement with earlier investigations a tendency to a moderate, uncompensated acidosis was found (YLPPÖ, RÄIHÄ, BRANNING, WILSON and co-workers, REARDON and co-workers). This tendency was, however, less pronounced for the subjects concerned here than has been the case in several of the earlier investigations. Thus REARDON and co-workers found an average of 45 volumes per cent for the CO_2 content in plasma and 7.31 for the blood pH. The reason for this discrepancy may be sought in the nutrition of the infant, the sampling conditions, and the laboratory procedures. Once again the difficulties of evaluating the CO_2 conditions in small infants must be pointed out. The results cannot be considered as directly representative of the situation under normal respiratory conditions, as the disturbances brought about by the sampling will assert themselves in greater or less degree.

A comparison of the values for infants given cow's milk and infants given mother's milk showed no difference in regard to the acidotic tendency. The material was, however, somewhat small for an adequate, general evaluation.

The metabolic acidosis in premature infants has been thought to have a bearing upon tissue hypoxia with an increased production of organic acids (RÄIHÄ). The possibility of a tissue hypoxia of this sort has, to some extent, been the reason for the protracted O_2 therapy which was formerly employed. It was therefore thought to be of interest to find out whether discontinuation of the O_2 administration would tend to accentuate the metabolic acidosis. The results gave no indication of this.

The O_2 Analyses

The wide spread in the values for the O_2 tensions will correspond to relatively small variations in the O_2 saturation. In most of the analyses the results should correspond to an O_2 saturation of about 90 per cent; in some cases, a little more. In 10 analyses (17 per cent) values were found to range between 50–55 mm Hg, i.e. the saturation should lie between 85–90 per cent.

The results indicate that the oxygenation of the blood must have been

relatively good in these prematures. This is in agreement with the results of the above-mentioned investigations by GRAHAM and co-workers and JONXIS. Furthermore, the present results show that the O_2 content of the cutaneous blood must have differed very little from that of the arterial blood.

Summary

Through gas analyses of cutaneous blood the author has tried to clarify the respiratory situation of premature infants. This first publication deals with the laboratory methods and the results obtained on premature infants without severe respiratory complications. Cutaneous blood samples obtained by heel puncture, 0.22 ml in volume, were employed in the analyses. Determinations of the CO_2 and O_2 tensions were carried out by equilibration of the sample with a small gas bubble. The equilibration and the gas analyses were carried out in the same apparatus, a Roughton-Scholander syringe. Part of the same sample was then transferred to a small glass tube for subsequent centrifuging and determination of the CO_2 content in plasma. Readings of the blood pH were made from Van Slyke's nomogram.

Eighty-eight determinations were carried out on 9 premature infants in the course of the first ten weeks after birth. The results gave no indication that a significant respiratory insufficiency existed in any of these cases. This conforms well with the results of earlier investigations on premature infants without respiratory complications. The average values for the entire material were: CO_2 tension, 39.4 mm Hg; CO_2 content in plasma, 50.5 volumes per cent; blood pH, 7.36. For the O_2 tensions most of the values were about 60 mm Hg, with no values below 50 mm Hg. However, the individual spread was relatively wide.

Détermination des gaz dans le sang de nourrissons prématurés.—I. *Recherches chez des nourrissons prématurés sans complications respiratoires.*

En analysant les gaz contenu dans le sang cutané l'auteur a tenté d'élucider le comportement de la respiration chez les nourrissons prématurés. Cette première publication traite des méthodes de laboratoire et les résultats obtenus chez des nourrissons prématurés sans complications respiratoires graves. On s'est servi, pour les analyses, d'échantillons de sang cutané obtenu par piqûre au talon et comportant au total 0,22 cc. Des dosages de la tension du CO_2 et de la tension de O_2 ont été effectués en équilibrant l'échantillon avec une petite bulle gazeuse. La mise en équilibre et l'analyse des gaz ont été faites dans le même appareil, une seringue de Roughton-Scholander. Une partie du même échantillon a alors été transféré dans un petit tube en verre pour centrifugation et dosage ultérieurs du CO_2 plasmatique. La lecture du pH sanguin s'effectuait à l'aide de nomogramme de van Slyke. Pendant les dix premières semaines après la naissance une série de 88 dosages ont été fait chez 9 nourrissons prématurés. Les résultats n'ont pas montré qu'il existait une insuffisance respiratoire marquée dans un de ces cas. Ceci est en concordance avec les résultats de recherches précédentes chez des nourrissons prématurés sans complications respiratoires. Les valeurs moyennes pour la série complète étaient : tension de CO_2 39,4 mm (Hg); contenu de CO_2 dans le plasma 50,5 volumes pour cent; pH sanguin 7,36. La plupart des taux de tension d'oxygène oscillait aux environs de 60 mm (Hg), aucune valeur étant inférieure à 50 mm (Hg). Les valeurs individuelles étaient cependant assez étalées.

Blutgasbestimmungen bei Frühgeburten. — I. Untersuchungen an Frühgeburten ohne Atemkomplikationen.

Der Verf. hat versucht, durch Gasanalysen von Kapillarblut die respiratorische Situation Frühgeborener zu erklären. Die vorliegende erste Veröffentlichung beschäftigt sich mit den Laboratoriumsmethoden und den Ergebnissen, die bei frühgeborenen Kindern ohne schwere Atemkomplikationen erreicht wurden. Für die Analysen nahm man Kapillarblutproben mit 0,22 ml, die durch Fersenpunktion gewonnen wurden. Bestimmungen der CO_2-Spannung und der O_2-Spannung sind durch Equilibration der Probe mit einer kleinen Gasblase durchgeführt worden. Die Equilibration und die Gasanalysen sind in demselben Apparat, einer Roughton-Scholander Spritze, ausgeführt worden. Ein Teil derselben Probe wird dann in ein kleines Reagenzglas zur darauf folgenden Zentrifugierung und Bestimmung des CO_2-Gehaltes des Plasmas überführt. Die Bestimmung des Blut-pH erfolgte im van Slykeschen Nomogramm. Eine Serie von 88 Untersuchungen wurde bei 9 Frühgeburten im Laufe der ersten zehn Wochen nach der Geburt durchgeführt. Die Ergebnisse ergaben keinen Hinweis dafür, dass in irgendeinem dieser Fälle eine deutliche respiratorische Insuffizienz vorlag. Dies stimmt gut mit den Resultaten früherer Untersuchungen bei Frühgeburten ohne Atemkomplikationen überein. Die Durchschnittswerte des gesamten Materials waren: CO_2-Spannung 39,4 mm (Hg), CO_2-Gehalt im Plasma 50.5 Vol %, Blut-pH 7,36. Für die O_2-Spannungen lagen die meisten Werte um 60 mm (Hg), keine Werte lagen unter 50 mm (Hg). Jedoch war die individuelle Streuungsbreite relativ weit.

Determinación de gases sanguíneos en prematuros. — 1. Investigación en prematuros sin complicaciones respiratorias.

El autor ha tratado de aclarar la situación respiratoria de los prematuros a través del análisis de la sangre periférica. En esta primera publicación se tratan los métodos de laboratorio y se comunican los hallazgos obtenidos en prematuros sin complicaciones respiratorias severas. Las muestras sanguíneas se obtuvieron por punción del talón en todos los casos usándose 0,22 ml. La tensión de CO_2 y de O_2 se tomaron equilibrando la muestra con una pequeña burbuja de aire. La equilibración y los análisis de gases fueron llevados a cabo con una jeringa de Roughton-Scholander. Parte de esta muestra fué transferida a un tubo de vidrio y centrifugada para determinar el CO_2 en el plasma. La lectura del pH sanguíneo se hizo usando el nomograma de van Slyke. Se hicieron 88 determinaciones en 9 prematuros durante las primeras 10 semanas de vida. Los resultados muestran que en ninguno de estos casos hubo insuficiencia respiratoria, lo cual está de acuerdo con resultados obtenidos en investigaciones anteriores. Los valores medios para todo el material fueron: tensión de CO_2 39.4 mm de Hg; contenido plasmático de CO_2 50,5 vol. %; pH sanguíneo 7.36. La mayoría de las tensiones de O_2 dieron valores alrededor de 60 mm Hg, no siendo ninguna cifra menor de 50 mm Hg. Sin embargo, las variaciones individuales son relativamente amplias.

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Paper Electrophoresis of Serum Proteins in Infantile Toxicosis

by C. CHOREMIS and CH. MOSCHIDIS

It is already well known that the elctrophoretic pattern of serum proteins is markedly disturbed during pathologic conditions which are characterized by an increased tissue destruction. Thus, Schedlowski and Scudder found an increase of alpha globulin in all severe inflammatory conditions, as well as in extensive tissue damage. They believe that the increase of the alpha globulin is the result of a reaction of the organism to pathologic processes, main feature of which is tissue destruction. Others (1, 2, 3) observed an increase of the alpha globulin after experimental burns, bone fractures, abscesses and the administration of ACTH. Koslowski, Hartmann and Voges, on the other hand, found that severe muscular injuries (Crush syndrome) produce a considerable hypoalbuminemia with an increase of the alpha and gamma globulins.

The present work was undertaken for the purpose of studying the electrophoretic pattern of serum proteins in toxicosis of infants during which there is not only a disturbance of fluid and electrolyte balance, but also tissue destruction.

Material and Methods

Altogether 30 infants with toxicosis, aged 1½–12 months, except one aged 3 years, were studied. The cases were classified according to their severity: *Group 1*, comprising 8 cases of moderate severity, and *Group 2*, comprising 22 severe cases.

The history previous to the present illness was approximately the same in all cases, i.e. there were diarrhea and vomiting for a few days (1–7). In 12 cases fever was present. In 4 there were also symptoms of respiratory infection.

All infants, except 2, were artificially fed. All of them had been full term babies with an average birth weight of 3000, except 3 who were prematures with a birth weight between 1900–2500 g.

On admission all cases showed dehydration of a moderate to severe degree: In the 1st group of the 8 moderately dehydrated patients, the clinical findings were: pallor, irritability, shining and sunken eyes, dryness of the skin and lips, poor turgor, tachycardia and hypertonicity. The 22 severely dehydrated infants (2nd group) presented: pallor, sunken fontanel, sunken eyes, dryness and diminished turgor of the skin, dried mucus membranes, retracted abdomen, loss of weight, marked tachycardia, collapsed

superficial veins, deep and sighing respirations, cold and blue extremities, lethargy and hypotonicity.

Two infants were desperately ill with full coma; they succumbed in a few hours after admission.

Treatment was started on admission and after the withdrawal of a sample of blood for electrophoretic studies and estimation of total serum protein.

Sodium chloride 0.85 % was administered parenterally with 5 % glucose solution, as well as M/6 sodium lactate. Darrow solution was administered orally on the 2nd and 3rd day. Plasma was not given at all, but small transfusions were administered in two cases. Parenteral fluid therapy, as a rule, lasted for 24 hours, in one case 36 hours, and in two cases 48 hours. Then the infants were fed with powdered skimmed milk, and from the 7th–10th day with half-cream powdered milk.

Antibiotics were given for a period of 5–8 days. The patients received mainly aureomycin, but in three cases in which aureomycin treatment was unsuccessful it was replaced by erythromycin. In four cases with pulmonary involvement, treatment was started with penicillin–streptomycin and later replaced by aureomycin.

Full recovery occurred on the average within 7 days in the 1st group, and within 10 days in the 2nd group.

The electrophoretic studies of serum were performed in barbiturate (veronal) buffer at PH 8.6 and ionic strength 0.1, using the Elphor H Electrophoretic instrument of Bender and Hobein. The paper strips were stained with saturated solution of amidoschwartz 10 B in Methyl Alcohol and acetic acid (9:1). We used Whatman No. 1 filter paper.

Total serum protein was determined by the Colorimetric Phenol Method of Folin and Ciocalteau, using the Leitz Photo-Electric Colorimeter.

The electrophoretic pattern was studied (1) on admission, before treatment was started (in all cases); (2) 8 days after admission (in 28 cases out of 30); (3) 15 days after admission (in 15 cases out of 30).

In addition to the electrophoretic studies, total serum proteins were estimated.

Results

Group 1 (toxicosis of moderate severity) included 5 infants aged $1\frac{1}{2}$–3 months and 3 infants aged $6\frac{1}{2}$–8 months.

On admission (before treatment was started) an increase of α_2-globulin was observed in all cases, highest 14.6 % (0.90 gm %), average 13.8 % (0.85 gm %), and a decrease of albumin, lower limit 44.7 % (2.68 gm %), average 51.9 % (3.11 gm %). In 6 cases α_1-globulin was elevated, highest 7.7 % (0.48 gm %), average 6.4 % (0.39 gm %). In two infants aged $6\frac{1}{2}$ and 7 months respectively an increase of gamma globulin was observed, average 23.5 % (1.46 gm %). Beta globulin fluctuated within normal values.

Total protein was above the normal level in 3 patients (average 6.63 gm %) and in the remaining 5 infants it was normal (average 5.80 gm %).

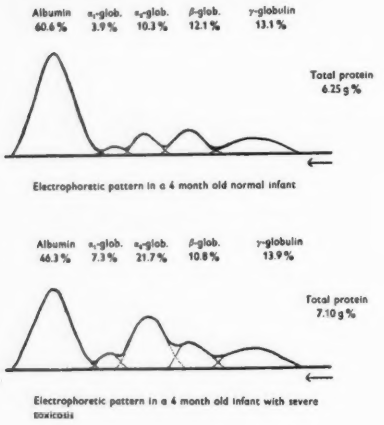
Albumin 60.6 %
α1-glob. 3.9 %
α2-glob. 10.3 %
β-glob. 12.1 %
γ-globulin 13.1 %
Total protein 6.25 g %
Electrophoretic pattern in a 4 month old normal infant
Albumin 46.3 %
α1-glob. 7.3 %
α2-glob. 21.7 %
β-glob. 10.8 %
γ-globulin 13.9 %
Total protein 7.10 g %
Electrophoretic pattern in a 4 month old infant with severe toxicosis

Fig. 1.

On the 8th day after admission in 4 cases, a slight decrease of α_1- and α_2-globulins was noted, as well as a slight increase of albumin, while in 4 others, values of α_1 and α_2 were unchanged and albumin revealed a further mild decrease. Beta and gamma globulins remained on the same levels.

Total protein values were on the low side (average 5.52 gm %) in all cases.

Average values of cases of this group are compared with values of normal infants in Table 1.

Group 2 (severe toxicosis) included 8 infants aged $1\frac{1}{2}$–3 months, 9 aged 4–6 months, 4 aged $9\frac{1}{2}$–12 months, and one child 36 months old.

On admission (before therapy was started) a considerable increase of α_2-globulin was noted in all cases, highest 21.7 % (1.45 gm %), average 16.9 % (1.12 gm %) and a decrease of albumin, lowest 41.7 % (2.79 gm %), average 49.0 % (3.28 gm %). The α_1-globulin was found to be elevated in 13 cases, highest 8.5 % (0.58 gm %), average 6.8 % (0.43 gm %). Beta globulin was within normal limits. Finally gamma globulin was markedly elevated in 3 cases, average 22.5 % (1.37 gm %) and diminished in 8 additional patients, average 11.1 % (0.75 gm %).

Values of total proteins in 15 cases were above the normal levels (average 7.19 gm %), in 3 cases they were found to be within normal limits (average 6.15 gm %), and in 4 additional cases they were subnormal (average 5.40 gm %).

On the 8th day after admission α_1- and α_2-globulins decreased somewhat, average of α_1-globulin 5.8 % (0.33 gm %) and of α_2-globulin 14.4 % (0.85 gm %). Albumin in most cases remained unchanged or decreased further.

TABLE 1.

Average values in two age groups of normal infants and of infants with moderate toxicosis.

	Percentage					Grams per cent					
	Albumin	Globulins				Total protein	Albumin	Globulins			
		α_1	α_2	β	γ			α_1	α_2	β	γ
	First group: 5 infants aged 1 1/2–3 months										
On admission . .	53.9	6.9	13.8	11.3	14.1	5.80	3.13	0.40	0.80	0.65	0.82
After 8 days . .	56.1	5.6	12.5	11.8	14.0	5.20	2.92	0.29	0.65	0.61	0.73
	Four normal infants aged 1 1/2–3 months										
	57.9 ± 2.4	4.5 ± 0.4	8.9 ± 1.2	11.8 ± 1.4	16.8 ± 1.7	6.0 ± 0.2	3.47 ± 0.14	0.27 ± 0.02	0.53 ± 0.07	0.70 ± 0.09	1.03 ± 0.10
	Second group: 3 infants aged 6 1/2–8 months										
On admission . .	48.4	5.5	13.5	12.0	20.6	6.63	3.23	0.39	0.88	0.79	1.34
After 8 days . .	52.1	4.9	9.5	12.0	21.5	5.82	3.03	0.29	0.56	0.71	1.23
	Four normal infants aged 6 1/2–8 months										
	59.8 ± 2.3	4.3 ± 0.4	10.5 ± 1.2	11.2 ± 1.3	14.2 ± 1.5	6.15 ± 0.2	3.7 ± 0.14	0.26 ± 0.02	0.64 ± 0.07	0.68 ± 0.08	0.87 ± 0.09

TABLE 2.

Average values in three age groups of normal infants and of infants with severe toxicosis.

	Percentage					Grams per cent					
	Albumin	Globulins				Total protein	Albumin	Globulins			
		α_1	α_2	β	γ			α_1	α_2	β	γ
	First group: 8 infants aged 1 1/2–3 months										
On admission . .	51.9	6.4	16.8	12.7	12.4	6.86	3.56	0.44	1.15	0.86	0.87
After 8 days . .	52.8	5.8	13.3	11.5	16.6	5.50	2.91	0.32	0.74	0.64	0.89
After 15 days . .	57.4	4.6	12.1	11.6	14.3	5.84	3.35	0.27	0.71	0.68	0.83
	Four normal infants aged 1 1/2–3 months										
	57.9±2.4	4.5±0.4	8.9±1.2	11.8±1.4	16.8±1.7	6.0±0.2	3.47±0.14	0.27±0.02	0.53±0.07	0.70±0.09	1.03±0.10
	Second group: 9 infants aged 4–6 months										
On admission . .	48.3	6.2	18.4	12.6	14.5	6.81	3.29	0.41	1.25	0.88	0.98
After 8 days . .	47.9	5.7	16.1	13.2	17.1	5.75	2.75	0.33	0.93	0.76	0.98
After 15 days . .	53.5	4.8	14.5	11.3	15.9	5.85	3.13	0.28	0.85	0.66	0.93
	Four normal infants aged 4–6 months										
	59.4±2.4	3.8±0.4	10.4±1.2	11.7±1.4	14.7±1.8	6.15±0.2	3.65±0.15	0.23±0.02	0.64±0.07	0.71±0.08	0.91±0.10
	Third group: 4 infants aged 9 1/2–12 months										
On admission . .	47.8	6.1	15.1	10.4	20.6	6.50	3.11	0.40	0.98	0.67	1.34
After 8 days . .	49.6	5.6	13.6	11.6	19.6	5.70	2.84	0.32	0.78	0.66	1.10
After 15 days . .	56.8	5.1	11.8	10.4	15.9	5.55	3.15	0.28	0.66	0.58	0.88
	Four normal infants aged 9 1/2–12 months										
	60.7±2.4	3.6±0.4	9.8±1.2	10.8±1.3	15.1±1.6	6.2±0.2	3.76±0.13	0.22±0.02	0.60±0.06	0.67±0.07	0.95±0.10

Beta globulin revealed no changes, while gamma globulin was elevated occasionally (4 cases) above normal levels.

The amount of total proteins was on the low side (average 5.78 gm %) in all cases.

On the 15th day after admission the albumin value increased, average 55.9 % (3.30 gm %). α_1- and beta-globulins were within the normal levels, while α_2-globulin was above normal, average 12.8 % (0.74 gm %). Finally gamma globulin, irrespective of the original value and the slight increase around the 8th day of treatment, was found to fluctuate within normal limits. In two cases gamma globulin remained elevated on the 15th day.

Total protein values were on the low side in all cases (mean 5.87 gm %).

Thus, by the end of the 2nd week, α_2-globulin remained slightly elevated and the albumin lagged in its restoration, while values of the remaining globulin fractions, in most cases, were found to fluctuate around normal levels.

Average values of cases of this group are compared with values of normal infants in Table 2.

Discussion

The study of serum proteins by paper electrophoresis in 30 infants suffering from toxicosis (severe diarrhea) reveals that the extent of the electrophoretic changes is proportional to the severity of the clinical picture.

During the acute stage of this syndrome there is a moderate or marked increase of the alpha globulin, especially of the α_2 fraction, and a decrease of the albumin. In a few cases the gamma globulin was also elevated.

During recovery (8th day and 15th day) the electrophoretic diagram shows a fall of alpha globulin and a rise of albumin; the electrophoretic pattern, however, does not return to normal until after the 8th day in moderately severe cases, and after the 15th day in the very severe ones. This is an indication that the electrophoretic changes are a result of the increased catabolism present in acute dehydration which, as already known, continues to take place after the subsidence of the clinical symptoms of dehydration.

The lack of a considerable hyperproteinemia during the acute stage, despite the obvious clinical signs of dehydration is probably due to the fact that the effect of dehydration is counterbalanced by (1) an increased toxic breakdown of protein, (2) a defective protein synthesis and (3) a hunger hypoproteinemia (ref. 5). Lastly, a mechanism similar to surgical shock seems to occur in severe cases, during which protein escapes to the tissues due to increased permeability of capillary membranes. As a result of this, serum protein not only does not rise, but occasionally reaches subnormal levels (5).

During recovery the absolute amount of total protein decreases as a rule. Since the absolute values are lower than in normal infants, we must admit that besides hydration other factors such as continued increased catabolism, defective protein synthesis and inadequate protein intake are needed to explain this low protein level.

Summary

The electrophoretic pattern of serum proteins has been studied in 30 infants suffering from toxicosis. During the stage of acute dehydration the main changes were a moderate or marked increase of alpha globulin, particularly of the α_2 fraction and a decrease of albumin. In some cases there was also an increase of the gamma globulin. During recovery the alpha globulin decreases while albumin increases. However, the return to normal of the electrophoretic pattern is not always achieved when clinical recovery occurs. The absolute amounts of total serum proteins have also been estimated and their significance has been discussed.

Electrophorèse sur papier des protéines du sérum au cours de la toxicose.

L'aspect électrophorétique des protéines du sérum a été étudié chez 30 enfants présentant une toxicose. Au cours de la période de déshydratation aigüe, on a pu noter une augmentation nette des alphaglobulines (en particulier la fraction alpha 2), et une diminution de l'albumine. Dans quelques cas, on a pu noter aussi une augmentation des gammaglobulines. La diminution des alphaglobulines, et l'augmentation de l'albumine est survenue avec la guérison. Néanmoins, le retour à la normale de la courbe d'électrophorèse n'est pas toujours achevé au moment de la guérison clinique.

Papierelektrophorese von Serum-Protein bei Säuglingstoxikose.

Die Elektrophoresebefunde von Serumproteinen sind bei 30 an Toxikose leidenden Säuglingen untersucht worden. Während des Stadiums der akuten Dehydration waren die Hauptveränderungen eine mässige oder ausgeprägte Zunahme des Alpha-Globulins, insbesondere der α_2-Fraktion und eine Abnahme des Albumins. In einigen Fällen bestand auch eine Zunahme des Gamma-Globulins. Während der Genesung nimmt das Alpha-Globulin ab, während das Albumin ansteigt. Jedoch ist der Rückgang zum normalen elektrophoretischen Bild nicht immer vollendet wenn die klinische Genesung eintritt.

Electroforesis en papel de las proteínas séricas en la toxicosis.

Se estudiaron las imágenes electroforéticas de las proteínas séricas en 30 lactantes afectos de toxicosis. Durante el período de deshidratación aguda, los cambios mas notables fueron un moderado o marcado aumento de la alfa globulina, especialmente de alfa 2. Durante la convalecencia, la fracción alfa globulina disminuyó mientras aumentaba la albúmina. Sin embargo, la vuelta a la imágen electroforética normal no siempre es completa al ocurrir, la mejoría clínica.

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Postoperative Studies of Pulmonary Stenosis without Aortic Overriding

by G. EKSTRÖM, Å. LUNDBERG and T. MÖLLER

Pulmonary stenosis constitutes almost 10 per cent of all congenital cardiac anomalies (1). At Kronprinsessan Lovisas Barnsjukhus in Stockholm congenital pulmonary stenosis without overriding of the aorta has been diagnosed by heart catheterization in about 100 children since 1947 (2).

This report is confined to cases with systolic pulmonary arterial pressure about 20–25 mm Hg and systolic right ventricular pressure at least 10 mm higher. In 69 children the right ventricular pressure exceeded 35 mm Hg, a reading which excludes doubtful borderline cases.

The clinical material is grouped into children with isolated pulmonary stenosis and those in which a septal defect was also present (Table 1). Cases with overriding of the aorta (tetralogy of Fallot) were not included. The first group was twice as large as the second. The sex distribution was similar in both groups. Five of the 45 children with isolated pulmonary stenosis and 11 of the 24 with a coexistent septal defect underwent operation.

Pulmonary stenosis may be valvular or infundibular in type. Mixed forms also occur. In order to force the blood beyond the stenosed channel and out into the pulmonary artery the pressure in the right ventricle must rise. In severe pulmonic stenosis with intact interventricular septum the right ventricular pressure is very high, considerably higher than that in the left ventricle. Frequently it exceeds 150–200 mm Hg. If a septal defect is also present, however, it acts as a safety valve to the left ventricle, thus reducing the right ventricular pressure. Because of the right-to-left venous shunt through the septal defect such children are cyanotic.

Children with moderately severe pulmonary stenosis have remarkably few symptoms. With severe stenosis and rising age there is an obvious diminution of physical capacity. If the pressure gradient between the right ventricle and the pulmonary artery is considerable, children with pulmonary

TABLE 1

Clinical material.

Pulmonary stenosis	Surgical treatment	No surgery	Total	
			♂	♀
Isolated	5	40	21	24
Combined with septal defect . .	11	13	12	12

♂ 33 (48 %); ♀ 36 (52 %); *total 69*.

stenosis and fairly large septal defects are more disabled than children with isolated pulmonary stenosis.

The degree of stenosis was classified as mild, moderate, severe and very severe. This classification was based on the right ventricular hypertension (Table 2). As expected, only a few of the children in the first group had reduced physical capacity or dyspnea. All of the children with severe stenosis had symptoms. Cyanosis does not occur in isolated pulmonic stenosis except in severe cases with cardiac decompensation. One of the children with moderate isolated stenosis was cyanotic. (It is probable that a septal defect existed which catheterization failed to reveal.)

All the children showed normal *somatic development*. In all but three the height and weight lay within the normal limits for Swedish children (3). In these three the measurements were somewhat above the variation limits.

The *physical sign* to which the greatest importance is attached is a coarse systolic murmur, best heard over the second left interspace. The second heart sound generally is weak. In 78 per cent of these children the systolic murmur was so loud that it could be felt as a thrill. Voussure was present in 17 per cent of the series.

The *electrocardiographic records* invariably showed signs of right cardiac hypertrophy when the right ventricular pressure exceeded 75 mm Hg.

The *roentgenograms* in most cases showed insignificant, if any, increase in cardiac volume. The configuration, on the other hand, displayed enlargment of the right ventricle in proportion to the severity of the stenosis. Also parallel with the stenosis were signs of impaired pulmonary circulation.

Heart *catheterization* was performed in all 69 children. Right ventricular pressure higher than 100 mm Hg was considered to indicate operation, even in asymptomatic cases. It has been observed that symptoms may commence abruptly and within a short time intensify until decompensation occurs. Operation was performed in a few children with severe symptoms and right ventricular pressure of 80–100 mm Hg.

TABLE 2

Anamnestic findings.

The figures in brackets denote the total number of children in each group.

Right ventricular pressure mm Hg	No. of cases	Reduced physical capacity or dyspnea	Cyanosis	
			Isolated pulmonary stenosis	Pulmonary stenosis + septal defect
(35–75) Mild stenosis	34	8	0 (24)	1 (10)
(75–150) Moderate stenosis. . .	28	18	1 (20)	3 (8)
(150–225) Severe stenosis . . .	5	5	0 (1)	2 (4)
(> 225) Very severe stenosis . .	2	2	0 (1)	1 (1)

In infundibular stenosis the surgical technique is more difficult and the results more doubtful than in valvular stenosis. It is therefore very important to determine the type of stenosis prior to operation. For this reason we performed *selective angiocardiography* in all children for whom surgery was contemplated.

The *operative procedure* employed was that introduced by BROCK (4), in which the dilating instrument is passed through the right ventricle into the stenosed area and the obstruction relieved by incision and dilatation. In infundibular stenosis the object is to resect the obstruction in the right ventricle. This dilatation of stenosed valves or resection of infundibular anomalies facilitates the passage of blood from the right ventricle to the pulmonary artery. Where there is a venous shunt through a septal defect, the shunt may diminish or cease, depending on the reduction of right ventricular pressure. Preoperatively present cyanosis then decreases or disappears.

To date there have been *no operative deaths* in our series.

In *postoperative follow-up* of patients with pulmonic stenosis the most reliable criterion of improvement is a fall in the right ventricular pressure. Ten of the 16 children submitted to surgery have since undergone heart catheterization.

The right ventricular pressures before and after operation are shown in Fig. 1. The preoperative pressure is represented by the total height of the column and the postoperative by the shadowed portion. The cases are arranged chronologically. The line at 30 mm Hg marks the upper limit of normal systolic pressure in the right ventricle. The line at 100 mm Hg shows the pressure above which operation was considered to be indicated.

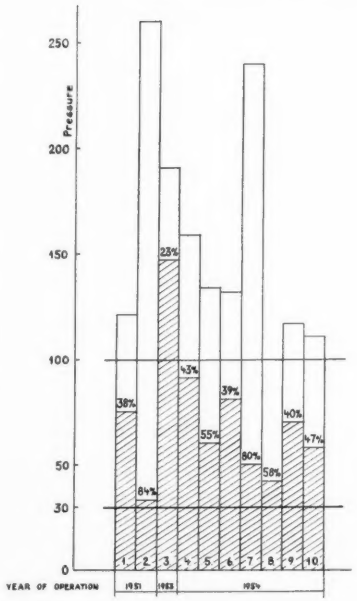


Fig. 1. Pressures in the right ventricle before and after operation.

Improvement was registered in all cases. The percentage reduction of pressure is stated in the columns. In two children the pressure fall was pronounced and in most of the others the postoperative readings were approximately half the preoperative. The result in Case 3 was unsatisfactory and re-operation is planned. This was the only case in which the right ventricular pressure after surgery was still above that accepted as indicating such intervention.

The postoperative changes are presented in Table 3. Improvement is marked +. Twelve of the 16 surgically treated children were readmitted to hospital for follow-up examination. In one case, however, the parents refused permission for heart catheterization. In another the right ventricular pressure could not be registered because of technical difficulties during catheterization. The pulmonary artery was not reached in postoperative catheterization of Cases 5 and 6. Table 3 also states whether the pulmonary stenosis was isolated or combined with septal defect. In Case 6 there was both infundibular and valvular stenosis. The postoperative observation period ranged from three weeks to more than three years. The physical capacity was improved in practically all the children. This aspect of the results was difficult to evaluate in one child (Case 8), who had been kept almost immobile at home for the six weeks following discharge from hospi-

TABLE 3

Postoperative findings in children treated for pulmonary stenosis.

Case No.	Name	Sex	Age at operation	Isolated or "combined" malformation	Postoperative observation period	Improvement in physical capacity	Altered murmur in PCG	Altered rigth hypertrophy in ECG	Pressure gradient rigth ventricle – pulm. artery Postoperative improvement (%)
1	B. P.	♀	13	comb.	3 w	+ +	0	0	47
2	Y. L.	♀	5	comb.	3 3/12	+ +	0 D	+	97
3	J. N.	♂	11	comb.	10/12	+	0	0	28
4	L. B.	♂	8	comb.	8/12	+ +	0	+	51
5	I. S.	♂	13	isol.	4/12	+	0	+	
6	S. H.	♂	13	comb.	5/12	+ +	0	+	
7	L. B.	♂	11	isol.	6 w	+ +	0 D	0	81
8	R. B.	♂	5	isol.	6 w	(0)	+	0	84
9	B. K.	♀	12	comb.	6 w	+	+	0	46
10	L. J.	♂	11	comb.	5 w	+	+	0	52
11	P. K.	♂	6	comb.	1 1/12	+	0	+	
12	L. W.	♂	4	comb.	11/12	+ +	+	+	

tal. The improved somatic status tallied well with the postoperative catheterization findings.

The systolic murmur was recorded by calibrated phonocardiography (5) before and after operation. No significant alteration of amplitude was noted. In a few cases the postoperative amplitude of the murmur was diminished in the latter half of systole.

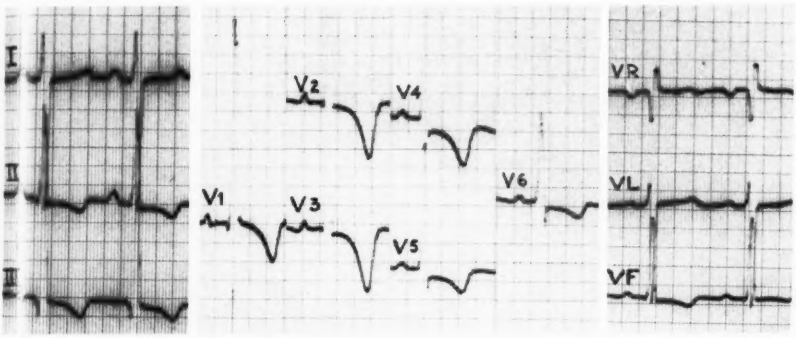
In two children a diastolic murmur (= D) was heard after operation (Cases 2 and 7), probably a sign of insufficiency of the pulmonic valves. There was no definite change in the weak second heart sound. Doubling of the sound also persisted after operation. This phenomenon is considered to be caused by retarded closure of the pulmonic valves (6).

Postoperative electrocardiography showed reduced hypertrophy of the right heart in almost half of the children. Such a reduction will probably be demonstrable in the remaining children when sufficient time has elapsed.

The difference between the right ventricular and pulmonary arterial pressures is a measure of the severity of the stenosis. This difference was less after operation. The percentage diminution of the pressure gradient is reported in the last column of Table 3. The children with the highest right ventricular pressures prior to operation showed the greatest postoperative improvement in this respect.

Electrocardiogram

Before operation.



2. Y. L. ♀ $3\,{}^{3}/_{12}$ years after operation.

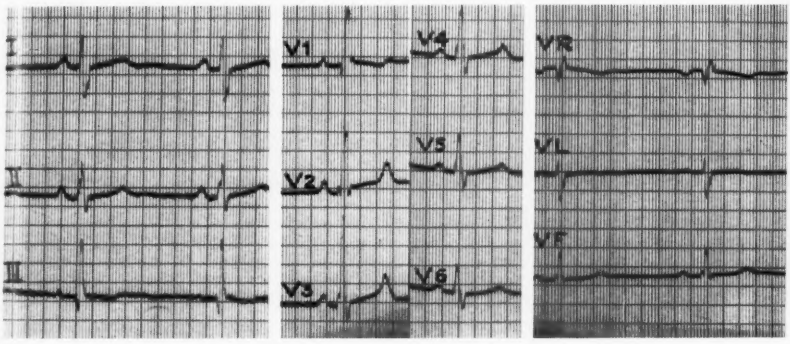


Fig. 2.

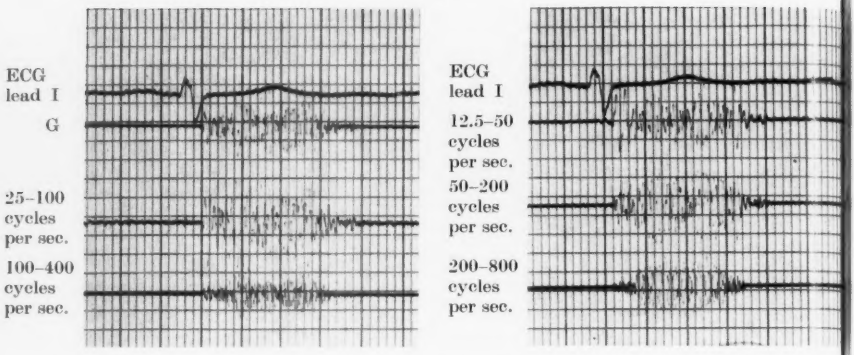
The cardiac *roentgenograms* showed strikingly little change after operation. In the cases with the longest observation period the cardiac volume decreased somewhat while the configuration remained unaltered.

The peripheral *oxygen saturation* during exercise and at rest was measured before and after operation in most of the children. The greatest improvements were seen in cases with a coexistent septal defect. This was probably due to reduction or cessation of the right-to-left shunt through the defect.

The postoperative electrocardiogram in Fig. 2 shows considerably decreased right cardiac hypertrophy and a tendency to normalization of the right axis deviation.

Phonocardiogram

Before operation.



9. B. K. ♀ Six weeks after operation.

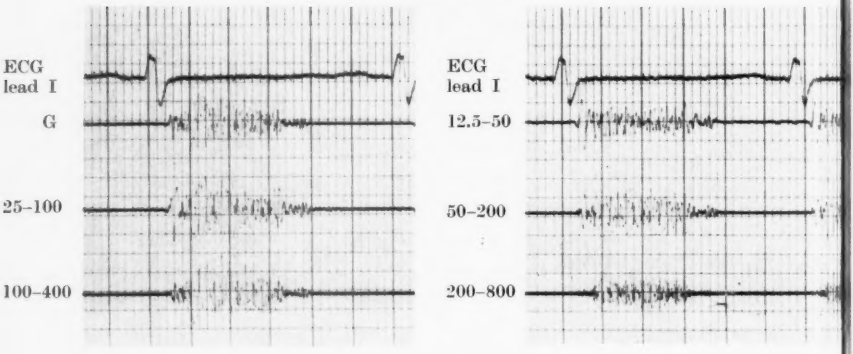


Fig. 3.

Phonocardiographic tracings after operation (Fig. 3) showed diminution and abbreviation of the systolic murmur in a few cases. The doubled and weak second sound was unchanged.

Selective angiocardiography was performed in Case 4 before and after operation. The catheter was introduced into the right ventricle. The dye injected through the catheter revealed narrowing of the pulmonary ostium, through which a thin jet of dye passed to the pulmonary artery. After operation the channel was decidedly wider. In this patient the right ventricular pressure decreased by 43 per cent.

Selective angiocardiography

a

b

Fig. 4. *a* Before operation. *b* After operation.

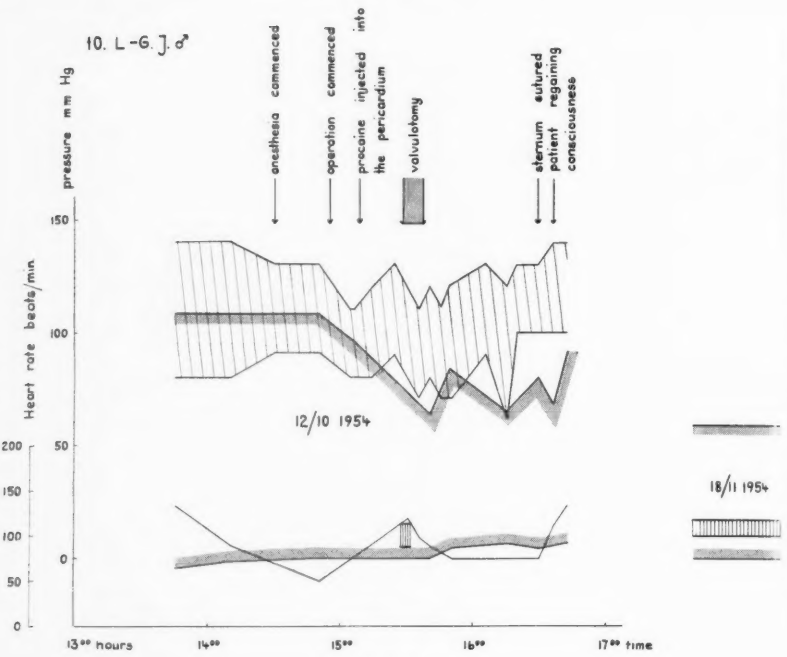


Fig. 5.

Catheterization during Operation

Continuous intracardiac pressure measurements were made during the operation in five cases. The catheter was passed into the right ventricle before the induction of anesthesia and was not removed until the patient had begun to recover consciousness. It was thus possible to record the intracardiac pressures during all phases of the operation (Fig. 5). In this diagram the ordinate shows the pressure in mm Hg and the abscissa the time. The thick lines signify the systolic and diastolic pressures in the right ventricle. The obliquely shaded area represents the amplitude of the peripheral blood pressure. The heart rate is recorded. The shaded rectangle shows the pressure in the pulmonary artery measured through a catheter directed by the surgeon into this vessel via the right ventricle. The pressures at heart catheterization five weeks after the operation are presented on the right of the figure.

The pressure measurements during operation in these cases are in good conformity with the findings of other workers (7, 8, 9, 10). The continuous pressure registration, however, indicated more clearly than occasional

readings obtained by cardiac puncture during the course of the operation that the results of surgery cannot be judged from such measurements. Accurate assessment of the results can be made only by comparing the pressures in the right ventricle and the pulmonary artery under basal conditions before and some time after surgery. The disturbance of the hemodynamic equilibrium entailed by an intervention of such magnitude is reflected in the pressure variations which occurred independently of valvulotomy.

Summary

Five of 45 children with isolated pulmonary valvular stenosis underwent surgical treatment and 11 of 24 with a coexistent septal defect. Cases of Fallot's tetralogy were not included. One patient had infundibular stenosis in addition to the valvular stenosis.

Operation was performed *ad modum* BROCK. Rapid subjective and objective improvement was recorded. Follow-up studies showed good results, in conformity with the findings of other writers (9, 11, 12, 13, 14, 15, 16).

Transarterial valvulotomy during hypothermia according to SWAN seems to give particularly encouraging results in this condition (8).

In most cases the postoperative observation period was relatively short. Continuous registration of right ventricular pressures during operation provided interesting data.

Etude post-opératoire de la sténose pulmonaire sans chevauchement de l'aorte.

Cinq enfants sur 45 présentant une sténose valvulaire pulmonaire isolée et onze enfants sur 24 présentant un défaut du septum concomitant, ont subi un traitement chirurgical. Des cas de tétralogie de Fallot n'ont pas été inclus. Un patient avait une sténose infundibulaire s'ajoutant à la sténose valvulaire. On a opéré suivant la technique de BROCK. Une amélioration subjective et objective rapide a été notée. Une étude de l'évolution ultérieure a montré de bons résultats, conformément aux résultats obtenus par d'autres auteurs. La valvulotomie transartérielle effectuée en état d'hypothermie suivant la méthode de SWAN, semble donner dans cette affection des résultats particulièrement encourageants. Dans la plupart des cas la durée d'observation post-opératoire était relativement courte. L'enregistrement continu des pressions ventriculaires droites pendant l'opération a fourni des renseignements intéressants.

Postoperative Studien von Pulmonalstenose ohne reitende Aorta.

Fünf von 45 Kindern mit isolierter valvulärer Pulmonalstenose wurden chirurgischer Behandlung unterzogen und 11 von 24 mit einem gleichzeitig bestehenden Septumdefekt. Fälle von Fallotscher Tetralogie wurden nicht mit einbezogen. Ein Patient hatte ausser der Valvularstenose eine Infundibularstenose. Die Operation wurde nach der Methode von BROCK durchgeführt. Schnelle subjektive und objektive Besserung konnte verzeichnet werden. Nachuntersuchungen zeigten in Übereinstimmung mit den Ergebnissen anderer Verfasser gute Resultate. Transarterielle Valvulotomie unter Hypothermie nach SWAN scheint bei diesem Zustand besonders ermutigende Erfolge zu ergeben. In den meisten Fällen war die postoperative Beobachtungszeit verhältnismässig kurz. Fortlaufende Druckmessung im rechten Ventrikel während der Operation ergab interessante Werte.

Estudios postoperatorios de estenosis pulmonar sin aorta cabalgando.

Fueron operados 5 de 45 niños con estenosis pulmonar valvular aislada y 11 de 24 con un defeto septal coexistente. No se incluyen los casos con tetralogía de Fallo. Un paciente tenía estenosis infundibular que se sumaba a la estenosis valvular. Se usó la técnica de BROCK. Depués de la operación se comprobó rápida mejoría objetiva y subjetiva. Estudios posteriores mostraron buenos resultados en concordancia con los hallazgos de otros autores. Valvulotomía transarterial en el curso de hipotermia de acuerdo con SWAN parece dar buenos resultados en esta condición. En la mayoría de los casos el período de observación postoperatorio fué relativamente corto. El registro de la presión ventricular derecha durante la operación mostró datos interresantes.

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Experimental Approach to the Pathogenesis of Retrolental Fibroplasia. V. The Influence of the State of Nutrition on Oxygen-Induced Changes in the Mouse Eye.[1]

by BO E. HELLSTRÖM

Introduction

A number of studies have indicated that exposure to high oxygen concentrations is an important environmental factor in the etiology of retrolental fibroplasia (for references see GYLLENSTEN and HELLSTRÖM (12)). Other studies have failed to show such a correlation, the most recent ones by ZACHARIAS *et al.* and ENGLE *et al.* The preliminary report of the cooperative study (KINSEY *et al.*), however, seems to support the role of oxygen in a decisive way. It does not appear justifiable, on the other hand, to claim that oxygen is the only cause of the disease, for in some cases reported no supplemental oxygen has been given (DANCIS *et al.*, BEMBRIDGE *et al.*, COXON).

No environmental factor except oxygen has been proved to be correlated to a higher incidence of the disease, and the studies of HEPNER & KRAUSE and HEPNER indicating a high electrolyte and fluid supply as being of etiological importance need confirmation. It does, however, seem likely that the hitherto unknown metabolic process regulating both normal and pathological growth of retinal vessels is influenced by factors other than oxygen exposure.

As for the host, there is no disagreement that prematurity is a predisposing factor, and according to ZACHARIAS *et al.* the birth weight and gestational age vary inversely with the incidence and severity of retrolental fibroplasia. It is not understood, however, why one child develops the disease, while another of the same birth weight and gestational age and during the same environmental conditions may escape it.

[1] This study was aided by grants from the Swedish National Medical Research Council.

The growth of prematurely born infants with and without the disease has been studied by LUBCHENCO *et al.* The infants in whom retrolental fibroplasia developed were the smallest babies at birth. Furthermore they lost weight for a longer period of time, but as they approached maturity they were gaining weight at a faster rate than the standard intrauterine median. Those in whom retrolental fibroplasia did not develop were larger at birth and were following the more gradual intrauterine curve, when they reached 40 weeks of gestational age. In eight out of nine multiple pregnancies, the smaller baby showed the more severe disease.

Thus it seems, as was pointed out by GORDON in the discussion of this paper, that retrolental fibroplasia occurs especially among babies who are small for the degree of their prematurity.

The close resemblance between the early pathologic picture of retrolental fibroplasia and the microscopic findings in the eyes of oxygen-exposed animals has been pointed out in several papers, PATZ *et al.*, ASHTON *et al.* (1, 2), GYLLENSTEN and HELLSTRÖM (9, 10), GERSCHMAN *et al.* In a previous report (GYLLENSTEN and HELLSTRÖM (10)) it has been shown that the oxygen-induced disease of the mouse eye occurs most frequently when newborn mice are exposed, the incidence rapidly falling with advancing age of the animals. Thus also in the experimental disease the incidence is inversely correlated to the maturity.

The question as to whether nutrition and growth might influence the oxygen-induced disease in animals of a certain age has not been systematically investigated. In an experimental study by MICHAELSON *et al.*, where newborn mice were exposed to 40 to 70 per cent of oxygen, a complete absence of capillaries in the retina was noted only in underdeveloped animals. As was stated by the authors this finding might imply that the retina of underdeveloped animals is particularly sensitive to hyperoxia; or else that the retina and the rest of the body were comparably affected by the hyperoxia. A third possibility remains to be excluded, namely that neither the underdevelopment nor the absence of retinal vessels was caused by the oxygen exposure.

The effect of starvation to death on the histologic structure of the retina in adult rabbits was studied by DELLAPORTA who found degenerative changes most regularly in the nuclear layers. Nothing is stated concerning the influence on retinal vessels.

The young mice exposed to concentrated oxygen in our experiments previously reported (GYLLENSTEN and HELLSTRÖM (9, 10)) generally showed a somewhat slower gain in weight than corresponding control animals. This was especially true of animals continuously exposed to oxygen for a longer period of time.

The present study was undertaken with the view of observing the influence of the state of nutrition on the oxygen-induced disease of the mouse eye. Previously an inhibition of the outgrowth of retinal vessels in animals continuously exposed to concentrated oxygen has been reported. As mentioned above these animals showed a relatively slow gain in weight. To ascertain that this inhibited outgrowth was not due to less nutrition *per se* the effect of starvation without oxygen exposure was also explored.

Finally it was felt that a study along these lines might possibly aid in throwing light on the complex mechanisms leading to retrolental fibroplasia in premature infants.

Material and Methods

The same experimental animals as in previous studies were used (black mice, stock C 57 BL/6, Roscoe B. Jackson Memorial Laboratory). The standard feeding, the methods for the exposure to oxygen, the checking of the oxygen concentrations and the histologic technique were the same as previously reported (GYLLENSTEN and HELLSTRÖM (9)). The exposure to oxygen began within 16 hours after birth. The oxygen concentrations were kept at 98 to 100 per cent. If the animals were supposed to stay in air following oxygen exposure the withdrawal took place within a few minutes. The newborn litters were grouped together in the way that mice from the same litters as the experimental animals were used as controls. The mothers of the young exposed to oxygen were interchanged every second day with mothers of the control litters. The lessened nutrition of the young was effected by separating the mothers from the litters every third day, and by making the group nourished by one mother numerically larger that the ordinary size of a litter. The "overfeeding" on the other hand was brought about by diminishing the same group (2 to 4 animals instead of the average 6 to 8).

The following experiments were undertaken:

Group A.—To study the influence of lessened nutrition on the normal vascularization and differentiation of the retina, some animals were starved as outlined above without any oxygen exposure and killed at 5, 10 and 15 days of age. The histologic picture of the retina was compared with that of some of the control animals. The experimental animals were weighed before being killed and the weight calculated in percentage of the average weight of corresponding control animals. Thirty-three animals survived.

Groups B–F.—In previous investigations a duration of 5 days exposure to oxygen, followed by 10 days stay in air was commonly used as a "standard method". In the present study the oxygen exposure was extended to 10 days, as the normal vascularization of the retina in these animals is completed or nearly completed at this age (MICHAELSON *et al.*). The deviations concerning the extent of vascular outgrowth in the experimental animals may therefore be easier to grade at this age. From previous experiences (GYLLENSTEN and HELLSTRÖM (9, 10, 11)) an inhibited outgrowth in the oxygen-exposed animals was to be expected. Some of the animals were killed after 10 days subsequent stay in air to evaluate the influence of the state of nutrition on the vasoproliferative phase as well.

TABLE 1

Mortality rates

	Mortality per cent
Group A (less nutrition)	60
Groups B, D and E (less nutrition and oxygen exposure with or without subsequent stay in air	77
Groups C and F (overfeeding and oxygen exposure with or without subsequent stay in air)	38
Control animals	26

Group B. Less nutrition during oxygen exposure for 10 days. Seventeen animals survived.

Group C. Overfeeding during oxygen exposure for 10 days. Thirteen animals survived.

Of the *control animals* 30 were killed at the age of 10 days.

Group D. Less nutrition during 10 days oxygen exposure, but not during a subsequent stay of ten days in air. Twelve animals survived.

Group E. Less nutrition both during 10 days oxygen exposure and a subsequent 10 day's stay in air. Fourteen animals survived.

Group F. Overfeeding both during 10 days oxygen exposure and a subsequent 10 days' stay in air. Twelve animals survived.

Of the *control animals* 19 were killed at the age of 20 days.

The mortality rate (Table 1) was considerable in all groups especially among the starved animals. This was due to the starvation, the general toxic effect of oxygen and the tendency to cannibalism increased by the interchanging of mothers etc. The varying mortality rates make a statistical comparison of the data difficult.

Results

The lessened nutrition of the animals as brought about in the experiments led to a considerable reduction of the gain in weight with advancing age, reducing the weight to about half the one of the control animals. The influence of this lessened nutrition without oxygen exposure (Group A) on the differentiation of the eyes was studied. The outgrowth of vessels of the nerve fibre layer was retarded, but only to a slight degree, and at 15 days of age it had extended to the ora in 9 of 11 starved animals. In the control animals this had occurred already at 10 days of age (Figs. 1 and 2). The retardation was evident also concerning other qualities of the differentiation of the eye, such as the separation of nuclear layers, the relative increase of the inner plexiform layer, the outgrowth of rods and cones, the development of secondary vitreous and the involution of hyaloid vessels. In addi-

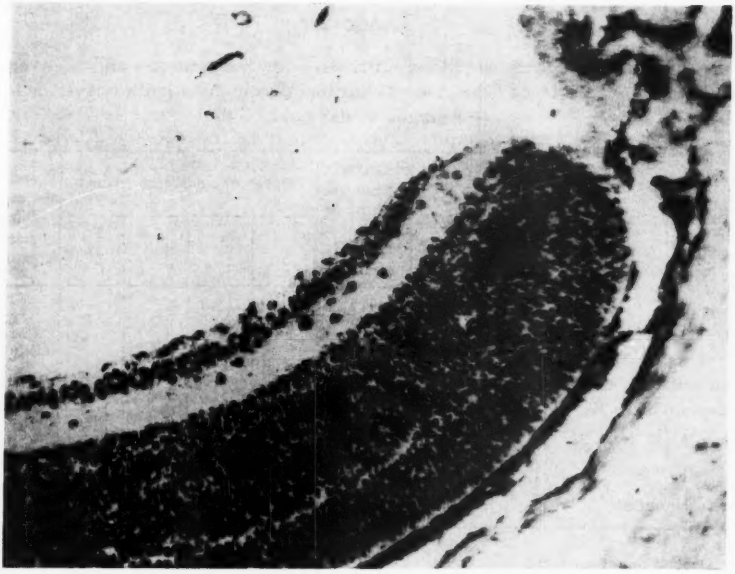

Fig. 1. Peripheral part of the retina in a 10-day-old starved animal. Incomplete separation of nuclear layers and retarded outgrowth of vessels in the nerve fibre layer. (× 225)

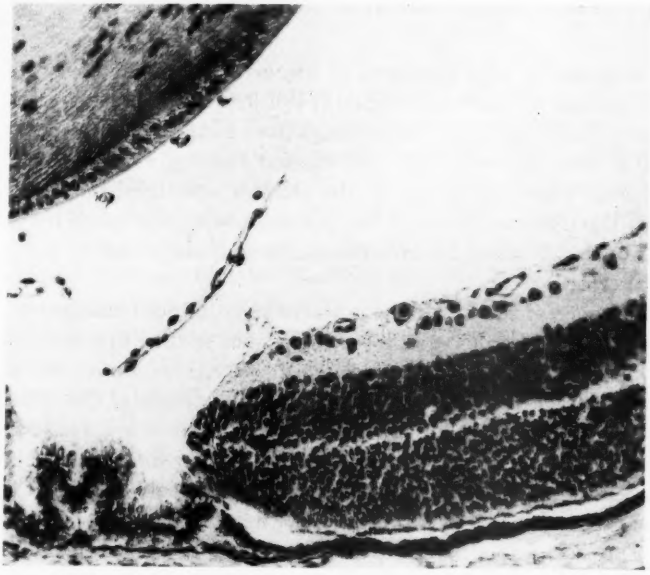

Fig. 2. Peripheral part of the retina in a 10-day-old control animal. Nuclear layers separated, normal capillaries in the nerve fibre layer. (× 225)

TABLE 2

Influence of (1) less nutrition, (2) less nutrition + oxygen exposure and (3) overfeeding + oxygen exposure on the vascularization of the nerve fibre layer in mice. Animals 10 days old.

	Number of animals	Mean and range of weight in per cent of control animals	Degree of vascularization*				Hyperplasia of vessels of nerve fibre layer
			0	+	+ +	+ + +	
Less nutrition (Group A) . .	10	55 (28–80)	0	0	7	3	0
Less nutrition + oxygen exposure (Group B)	17	64 (38–96)	17	0	0	0	0
Overfeeding + oxygen exposure (Group C)	13	152 (85–188)	12	1	0	0	0
Control animals	30	–	0	0	0	30	0

* Degree of vascularization:

0 = No vessels in the nerve fibre layer.

\+ = Vessels extending in the first third of the distance optic disc to ora.

\+ + = Vessels extending in the second third of the same distance.

\+ + + = Vessels extending in the last third of the same distance.

tion, a remarkably high incidence of hemorrhages in the nerve fibre layer occurred among the starved animals (14 of 33). Among the control animals this occurred in 4 per cent. No degenerative changes of the cell elements of the retina were observed with the routine histologic technique used, not even in cases where the weight of the animals amounted to a fourth of the controls. The different layers of the retina showed only small irregularities, as was frequently found in control animals and was probably partly due to technical errors.

The influence of the nutrition on the oxygen-induced changes of the eyes in animals exposed to oxygen for 10 days was studied in Groups B and C. Since the development and behaviour of the retinal vessels are of special interest with regard to the early pathology of retrolental fibroplasia, these have been specified in Table 2, where also the finds in starved, non-oxygen exposed 10-day-old animals are found, for comparison. From this table it can be seen that the oxygen exposure causes a complete, or almost complete, inhibition of outgrowth of retinal vessels, irrespective of the state of nutrition. In no case was a pathological hyperplasia of the vessels of the nerve

TABLE 3

Influence on the vascularization of the nerve fibre layer and on the occurrence of pathological proliferation of retinal vessels in newborn mice exposed to oxygen for 10 days, followed by a stay in air for 10 days through (1) less nutrition during oxygen exposure only, (2) less nutrition both during oxygen exposure and subsequent stay in air, and (3) overfeeding both during oxygen exposure and subsequent stay in air.

	Number of animals	Mean and range of weight in per cent of control animals	Degree of vascularization*				Hyperplasia of vessels of nerve fibre layer
			0	+	+ +	+ + +	
Less nutrition during oxygen exposure (Group) D) . . .	12	79 (62–97)	0	9	3	0	12
Less nutrition during oxygen exposure and subsequent stay in air (Group E) . . .	14	38 (23–70)	6	8	0	0	2
Overfeeding during oxygen exposure and subsequent stay in air (Group F) . . .	12	105 (51–153)	2	7	3	0	7
Control animals	19	–	0	0	0	19	0

* Degree of vascularization: See Table 2.

fibre layer noted. In a few cases small bundles of endothelial cells, without visible lumina and probably representing angioblasts, were found. In addition to the findings tabulated, persistence and probably proliferation of the hyaloid vessels occurred to the same extent among starved and overfed. The absence of hemorrhages in the nerve fibre layer was remarkable as compared to the high incidence among the starved but not oxygen-exposed animals. Hemorrhages in the vitreous body occurred in 4 of 17 starved and oxygen-exposed animals as compared to an incidence of 1 of 13 among the overfed. No abnormal irregularities of the layers, no atrophy or folding of the retina were found in either groups.

The influence of the nutrition on the oxygen-induced changes in animals exposed to oxygen for 10 days, followed by a stay in air for 10 days, was studied in Groups D, E and F. The outgrowth of retinal vessels and the occurrence of pathological proliferations from these vessels are described in Table 3. As has already been reported in previous papers (GYLLENSTEN and HELLSTRÖM (9, 10)) a vasoproliferous stage occurs when the animals are

Fig. 3. Lessened nutrition both during 10 days' oxygen exposure and a subsequent 10 days' stay in air (Group E). Persistence of hyaloid vessels, otherwise normal eye. (× 40)

transferred to air. From Table 3 it is clear that this vasoproliferous phase is influenced by the state of nutrition, especially concerning the occurrence of pathologic hyperplasia of retinal vessels with budding into the vitreous body. This was apparently depressed by continued starvation during the stay in air, being apparent in only 2 out of 14 animals, as compared to an incidence of 12 out of 12 in animals starved only during the oxygen exposure (Figs. 3–7). This difference is highly significant also from a statistical point of view, using MAINLAND's exact significance tables. The mortality rates in these two groups were of similar magnitude. Among the overfed animals the incidence of pathologic hyperplasia of retinal vessels was 7 of 12.

In addition to the changes concerning the retinal vessels, the typical proliferation of hyaloid vessels as described in previous papers (GYLLENSTEN and HELLSTRÖM (9, 10)) occurred irrespective of the state of nutrition with hemorrhages into the vitreous body in all cases, whereas hemorrhages in the nerve fibre layer occurred only occasionally. A conspicuous difference between the groups was found regarding observed irregularities of retinal layers with folds and intermixing of nuclear layers. This was found to only a relatively slight degree among the animals, where starvation was continued during the stay in air, and where a pathologic growth of vessels in the nerve

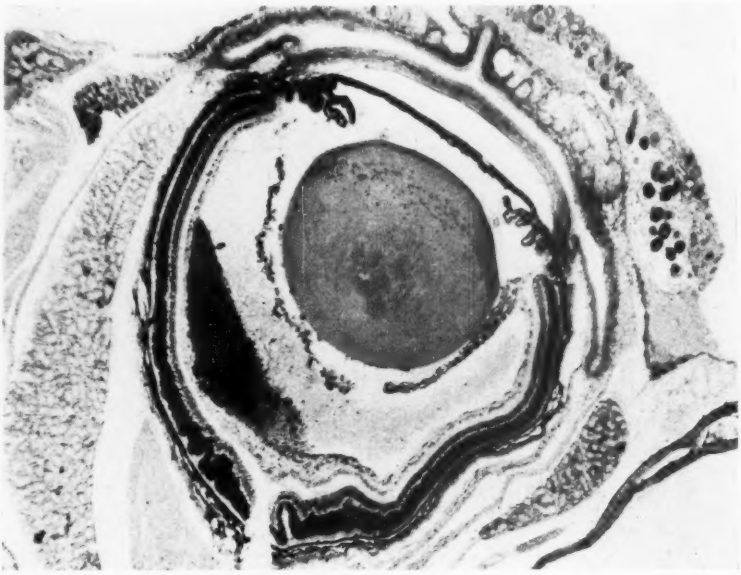

Fig. 4. Lessened nutrition during 10 days' oxygen exposure but not during a subsequent stay of 10 days in air (Group D). Persistence of hyaloid vessels, hemorrhage in the vitreous body, thickening of the central part of the retina with proliferous vessels in the nerve fibre layer and irregularities of the nuclear layers. (× 40)

fibre layer was also lacking (Fig. 6). A slight reduction of the thickness of some layers, especially the inner nuclear layer, was frequently observed, with no obvious relation to the state of nutrition, except for the layer of rods and cones. This was constantly underdeveloped in the groups where the animals were starved.

Discussion

From the above it seems clear that lessened nutrition, as might be expected, leads to a certain delay of the differentiation of the eye, including the vascularization of the nerve fibre layer. This retardation of the outgrowth of vessels is only relatively slight as compared to the inhibition occurring when newborn mice are exposed to oxygen. The frequent occurrence of hemorrhages in the nerve fibre layer in the starved animals probably points to a capillary damage or a clotting deficiency due to some qualitative deficiency of the nutrition. Similar hemorrhages have been a common finding also in animals exposed to general hypoxia (GYLLENSTEN and HELLSTRÖM (11)).

Fig. 5. Normal eye. Control animal 20 days old. (× 40)

The animals transferred to air following the oxygen exposure showed changes of the retinal and hyaloid vessels, hemorrhages and irregularities of retinal layers. If the normal gain in weight was depressed by lessened nutrition, both during oxygen exposure and subsequent stay in air, the abnormal vascular hyperplasia in the nerve fibre layer was also depressed. It is to be noted that this starvation, although being of a degree to reduce the weight to less than half the normal, did not influence the proliferation of hyaloid vessels in these cases.

In contrast, if the animals were allowed to regain weight at a relatively more rapid speed than normally during the stay in air, such an abnormal hyperplasia of retinal vessels occurred in all cases, that is even more frequently than in animals where the absolute gain in weight was kept above normal the whole time (Group F).

Furthermore there seemed to be a connection between absent vascular hyperplasia in the nerve fibre layer and less derangement of the nuclear layers. Thus the histologic picture of the retina in the continuously starved animals (Group E) seemed relatively normal as compared to an animal of e.g. Group D, where starvation was discontinued on transfer to air.

Some of the results described above are in agreement with the findings

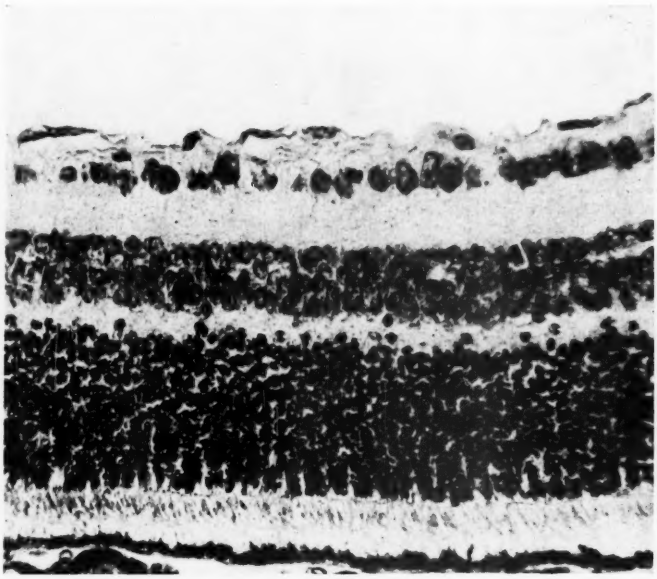

Fig. 6. Lessened nutrition both during 10 days' oxygen exposure and a subsequent 10 days' stay in air (Group E). No proliferous changes of vessels in the nerve fibre layer, regular nuclear layers. (× 450)

by MICHAELSON *et al.* who noted an inhibited vascular outgrowth in underdeveloped oxygen-exposed animals. However, there are also many dissimilarities. As these can be partly explained by the difference in oxygen concentrations used, they will be discussed in another paper, where the influence of different oxygen concentrations on the oxygen-induced changes of the mouse eye has been systematically explored (HELLSTRÖM (13)).

The starved animals probably also sustained some degree of dehydration and it must be kept in mind that this could be of equal importance as the actual lessened nutrition.

It has thus been shown that the oxygen-induced disease of the mouse eye can be influenced by the state of nutrition. There are however many objections against immediate analogies being drawn concerning the disease in premature infants. In the first place, as has been pointed out in previous papers, there is no identity between the experimental disease and retrolental fibroplasia. Secondly, the deviations from normal weight in the nutritional experiments described have been relatively large.

It may however be of significance that the hyperplastic changes of retinal vessels in the experimental disease occurred most regularly among animals

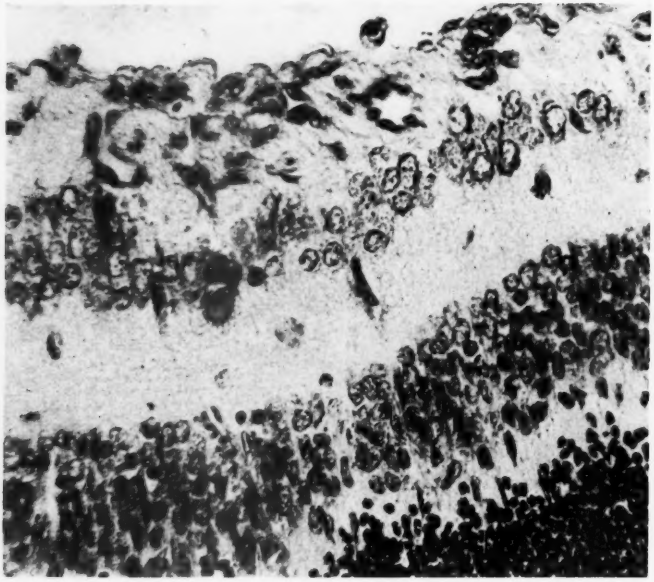

Fig. 7. Lessened nutrition during 10 days' oxygen exposure but not during a subsequent stay of 10 days in air (Group D). Thickened retina with proliferous changes of the vessels in the nerve fibre layer. (× 450)

starved in oxygen and rapidly gaining weight, approaching that of the controls, during the stay in air. It is interesting to compare this find with the statement by LUBCHENCO *et al.*, that retrolental fibroplasia occurred especially among infants not only with low birth weight and who had a greater weight-fall during the neonatal period, but subsequently were regaining weight at a relatively fast speed. However, these clinical observations need confirmation. It is possible, and in that case gratifying, that a more detailed study of this kind may be rendered impossible through the generally adopted restrictions in the administration of oxygen to premature infants.

Summary and Conclusions

1. The influence of the state of nutrition on the vascularization and differentiation of the retina and on the oxygen-induced disease of the eyes in newborn mice was studied.

2. In starved animals a relatively slight retardation of the outgrowth of vessels in the retina was found together with other signs of delayed differentiation and frequent hemorrhages in the nerve fibre layer.

3. The state of nutrition did not influence the inhibition of the outgrowth of retinal vessels following oxygen exposure.

4. Among animals transferred to air, following the oxygen exposure, less nutrition both during the stay in oxygen and in air was found to depress the pathological proliferation of vessels in the nerve fibre layer, whereas the proliferation of hyaloid vessels was uninfluenced.

5. Proliferation of vessels in the nerve fibre layer was most frequently seen in animals starved during the oxygen exposure, and with a relatively rapid gain in weight during the subsequent stay in air.

6. The significance of these finds with regard to retrolental fibroplasia in premature infants is discussed.

Contribution expérimentale à la pathogénie de la fibroplasie rétrolentale. V. Influence des conditions de nutrition sur les modifications produites par l'oxygène sur l'œil de la souris.

Chez des animaux soumis à une restriction alimentaire, on a noté un léger retard du développement des vaisseaux rétiniens, ainsi qu'une différentiation tardive et de fréquentes hémorragies dans la couche des fibres nerveuses. Les conditions de la nutrition n'ont pas influencé l'inhibition du développement des vaisseaux rétiniens qu'entraine l'exposition à l'oxygène. Chez des animaux d'abord soumis à l'oxygène puis transférés à l'air, une diminution de la nutrition — tant au cours de l'exposition à l'oxygène qu'à l'air — a entrainé une diminution de la prolifération pathologique des vaisseaux dans la couche des fibres nerveuses, alors que la prolifération des vaisseaux hylaoïdes n'était pas modifiée. La prolifération des vaisseuax dans la couche des fibres nerveuses a été observée plus souvent chez des animaux soumis à une restriction alimentaire au cours de leur séjour dans l'oxygène, et montrant ensuite un rapide gain de poids à l'exposition à l'air. La signification de ces résultats est discutée par rapport à la fibroplasie rétrolentale des prématurés.

Experimenteller Beitrag zur Pathogenese der Retrolentalen Fibroplasie. V. Der Einfluss des Ernährungszustandes unter wechselnder Sauerstoffzufuhr auf das Mäuseauge.

Bei verhungerten Tieren wurde eine relativ leichte Verzögerung der Sprossung von Gefässen in die Netzhaut zusammen mit anderen Zeichen einer verzögerten Differenzierung und häufigen Blutungen in der Nervenfaserschicht gefunden. Der Ernährungszustand beeinflusste nicht die Hemmung des Wachstums der Retinagefässe, das der Sauerstoffzufuhr folgte. Bei Tieren, die nach Aufenthalt in Luft Sauerstoff ausgesetzt wurden, stellte man fest, dass reduzierte Nahrungszufuhr, während sowohl Aufenthalt in Sauerstoff wie in Luft, die pathologische Proliferation der Gefässe in die Nervenfaserschicht verminderte, wogegen die Proliferation von hyaloiden Gefässen unbeeinflusst war. Die Proliferation von Gefässen in die Nervenfaserschicht wurde am häufigsten bei Tieren gesehen, die während Sauerstoffaussetzung gehungert hatten und während des nachfolgenden Aufenthaltes in Luft relativ schnell an Gewicht zugenommen hatten. Die Bedeutung dieser Befunde im Hinblick auf die retrolentale Fibroplasie bei Frühgeburten wird besprochen.

Intento experimental de aclarar la patogénesis de la fibroplasia retrolental. V. Influencia del estado nutricional en las alteraciones provocadas por oxígeno en los ojos de rata.

En animales hiponutridos, un retardo relativemente pequeño en el crecimiento de los vasos de la retina se encontró junto con otros signos de diferenciación retardada y

frecuentes hemorragias en las fibras del nervio subyacente. El estado de nutrición no influenció la inhibición de la proliferación de los vasos de la retina siguiendo exposición al oxígeno. En animales transferidos al aire después de la exposición a oxígeno, la hiponutrición durante ambos períodos mostró deprimir la proliferación de vasos en el lecho nervioso mientras no se modificaba la proliferación de los vasos de la hialoide. En animales hiponutridos durante la exposición al oxígeno y con un relativamente rápido aumento de peso durante la subsecuente exposición al aire, la proliferación de las fibras del lecho nervioso se vió mas frecuentemente. Se discute la significación de estos hallazgos en relación con la fibroplasia retrolental en el prematuro.

The technical assistance by Miss INGER ALNÖ is gratefully acknowledged.

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From the Children's Hospital, University of Oslo, Norway
(Head: Professor Leif Salomonsen)

A Comparison of Hemoglobin and Erythrocyte Values in the First-born and the Second-born Twin, and in First, Second and Third Triplet during the Neonatal Period

by MARTIN SEIP

The observation was made by the author that in the first week of life the first-born twin (twin no. 1) frequently has lower hemoglobin and erythrocyte values than his twin brother or sister (twin no. 2). We then decided to investigate in a series of newborn twins and triplets, whether a statistically significant difference in hemoglobin and erythrocyte level could be established between twin no. 1 and twin no. 2, or between triplet no. 1, triplet no. 2 and triplet no. 3, and, if such was the case, for how long a time after birth.

The patients studied were all twins and triplets treated in the Children's Hospital, University of Oslo, from the first week of life during the period Jan. 1947 to June 1955, and a number of twins born in the Maternity Hospital, University of Oslo during the months March to June 1955. Twenty-four pairs of twins and four sets of triplets are included. No blood disorders were found in these newborn infants which would influence the blood picture in a different way in one twin or triplet as opposed to the others. Similarly no significant abnormalities of the birth mechanism were observed. Two pairs of twins were for particular reasons not included. They will be discussed below.

The birth weights ranged from 1050 to about 3000 g, being less than 2000 g in one half of the cases. The course was uneventful during the period of observation in the great majority. However, a few infants belonging to the lowest weight group developed asphyxia of varying degree and duration. Such complications occurred with approximately the same frequency in the first-born and last-born twins (triplets no. 1, no. 2 and no. 3). Five infants died in the first week of life, pulmonary complications and cerebral hemorrhage being the causes of death. Of these five, one was born as no. 1, three as no. 2, and one as no. 3.

The blood picture was in all cases recorded at least once, occasionally twice during the first week of life. The first record was sometimes made as early as 12–24 hours after birth, but more often somewhat later, up to six days after birth. Those infants who were treated in the Children's Hospital (i.e. about half of the total number, and

particularly those weighing 2000 g or less at birth) were then reexamined at weekly intervals during the stay in hospital.

Blood for hemoglobin determinations and cell counts was taken from the heel. Hemoglobin was determined in per cent according to Haldane's standard with a Sicca hemometer. Red cells were counted in a Buerker counting chamber.

In 24 pairs of twins studied within six days after birth the hemoglobin level was higher in twin no. 2 than in twin no. 1 in 21 instances. It was the same in both twins in two instances. In one case only, twin no. 1 showed a slightly (7 per cent) higher hemoglobin percentage. The greatest difference in hemoglobin level recorded during the first week of life was 30 per cent. The average figures were:

Twin no. 1—121 % hemoglobin
Twin no. 2—132 % hemoglobin

The red cell counts were in good agreement with the hemoglobin determinations, the following averages being found:

Twin no. 1—5.41 mil./cmm
Twin no. 2—5.96 mil./cmm

In the four sets of triplets hemoglobin and erythrocyte values in all instances were higher in triplet no. 3 than in triplet no. 1. In triplet no. 2 the results were approximately as in triplet no. 1. The following averages were found:

Triplet no. 1: hemoglobin 132 %, red cells 5.13 mil./cmm
Triplet no. 2: hemoglobin 136 %, red cells 5.04 mil./cmm
Triplet no. 3: hemoglobin 144 %, red cells 5.55 mil./cmm

We may conclude that the last-born infant in a set of twins or triplets as a rule has higher hemoglobin and erythrocyte values than the first-born twin or triplet for some time after birth. Fig. 1 illustrates, for how long a time after birth this difference could be demonstrated in our series. It will be seen that in the first two weeks of life almost all hemoglobin values were higher in twin no. 2 (triplet no. 3) than in twin no. 1 (triplet no. 1).

From two weeks of age the values for twin no. 2 are distributed with almost the same frequency on either side of the values for twin no. 1.

The described difference in hemoglobin and red cell level during the first two weeks of life must be due, in the author's opinion, to the fact that the last-born twin or triplet receives an extra "blood transfusion" from the placenta and umbilical vessels after birth, before the clamping of the cord. As long as the uterine cavity still contains a fetus, the uterus will not be able to contract to the same extent as after the delivery of this fetus. The

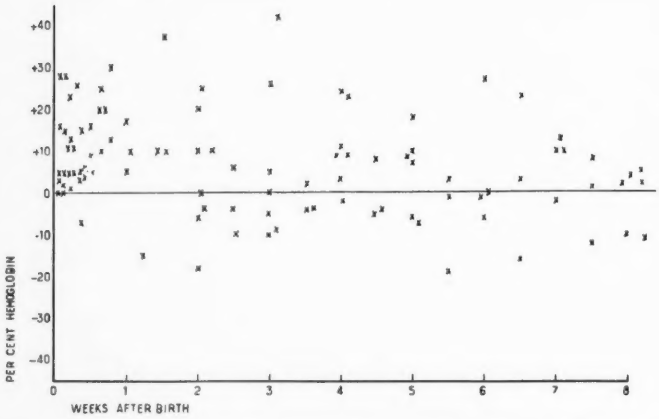

Fig. 1. The hemoglobin level in heel blood of second twin or third triplet (crosses) in relation to the hemoglobin level of first twin or triplet (solid line).

last-born twin or triplet therefore will receive more blood from the placental circuit, when the uterus contracts, and most of all when the clamping of the cord is somewhat delayed. The data presented above confirm the prevailing concept that the newborn may receive a considerable amount of extra blood after its birth, particularly by delayed clamping of the cord (De Marsh, Alt & Windle, Selander).

The following observations also indicate that the explanation presented above is the correct one. In two twin births which are not included in the main series, twin no. 2, for particular reasons, could not receive the extra "blood transfusion" from the placenta.

At birth one of these had the cord wrapped twice around his neck so tightly that the umbilical vein had obviously been compressed before birth. He suffered from severe asphyxia. In this case the blood values on the second day of life were as follows: In the "normal" twin no. 1, who did not have the cord around his neck, hemoglobin 160 per cent, red cells 6.68 mil./cmm. In twin no. 2, hemoglobin 110 per cent, red cells 5.56 mil./cmm.

In the second pathological case the mother was brought to the Maternity Hospital with a copious vaginal hemorrhage. Placental separation was found to be present. The placenta was delivered almost immediately after the birth of twin no. 2. On the seventh day of life the following blood values were found: Twin no. 1, hemoglobin 130 per cent, red cells 5.40 mil./cmm. Twin no. 2, hemoglobin 110 per cent, red cells 4.72 mil./cmm.

The findings reported may be of some clinical importance. A newborn infant has its most important iron reserve in its high content of circulating hemoglobin. This iron reserve, birth weights being of the same order of

magnitude, is assumed to be greater in twin no. 2 (triplet no. 3) than in twin no. 1 (triplets nos. 1 and 2). Furthermore, the last-born twin or triplet probably will be predisposed to a somewhat higher serum bilirubin level in the neonatal period, owing to its greater amount of circulating hemoglobin (Weech).

Summary

The last-born twin or triplet usually has a higher hemoglobin and erythrocyte content of the peripheral blood during the first two weeks of life than twin no. 1 (triplets nos. 1 and 2). This is assumed to be due to an extra "blood transfusion" to the last-born twin or triplet from the placenta and umbilical vessels after birth, before the clamping of the cord, caused by the more complete contraction of the uterus when the last fetus is also delivered. The last-born twin or triplet therefore is likely to have a somewhat greater iron reserve at birth.

Comparaison du taux d'hémoglobine et du nombre d'érythrocytes pendant la période néonatale chez le premier et le deuxième jumeau, le premier, le deuxième et le troisième triplet.

Pendant les deux premières semaines de la vie, le sang périphérique est plus riche en érythrocytes et en hémoglobine chez le jumeau ou le triplet dernier-nés que chez le premier jumeau (ou le 1er et le 2e triplet). Ce fait est expliqué parce que le jumeau ou le triplet dernier-nés reçoivent, avant le clampage du cordon, une transfusion supplémentaire de sang venant du placenta et de l'utérus, celui-ci se contractant de manière plus complète après la délivrance du dernier fétus. Le jumeau ou le triplet dernier-nés sont susceptibles, par conséquent, d'avoir une réserve de fer plus considérable.

Ein Vergleich von Haemoglobin- und Erythrocytenwerten zwischen erst- und zweitgeborenen Zwillingen und erst-, zweit- und letztgeborenen Zwillingen während der Neugeburtsperiode.

Der zuletzt geborene Zwilling oder Drilling hat gewöhnlich einen höheren Haemoglobin- und Erythrocytengehalt im peripheren Blut während der ersten zwei Lebenswochen als der Zwilling Nr. 1 (Drilling Nr. 1 und 2). Es wird angenommen, dass dies durch eine besondere „Bluttransfusion" bedingt ist, die der letztgeborene Zwilling oder Drilling nach der Geburt von der Placenta und den Nabelgefässen bekommt, bevor die Nabelschnur durch die vollständigere Kontraktion des Uterus abgedrosselt wird, wenn auch der letzte Foetus geboren ist. Der letztgeborene Zwilling oder Drilling muss deshalb wahrscheinlich bei Geburt eine etwas grössere Eisenreserve haben.

Comparación de los valores hemoglobínicos y eritrocíticos en el primero y segundo mellizo y en el primero, segundo y tercer trillizo durante el periodo neonatal.

Durante las dos primeras semanas de vida, los valores de hemoglobina y el recuento de eritrocitos en la sangre periférica son generalmente mas altos en el mellizo o trillizo nacido último. Se cree que esto sea debido a una transfusión extra por parte de la placenta y los vasos umbilicales antes de una contracción más completa del útero. Probablemente el último mellizo o trillizo sea, al nacer, portador de una mayor reserva de hierro.

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Incidence and Significance of Heart Murmurs in Newborn Infants

by ÅKE GYLLENSWÄRD

It is a common experience among pediatricians that even loud heart murmurs heard during the neonatal period often disappear before a later examination. Such infants show no other signs of heart disease and develop normally. In this situation the physician has to cope with an intricate problem, i.e. whether or not a mother should be informed about such an observation in the newborn period. In the cases of unmistakable heart disease which show definite clinical symptoms besides heart murmurs, there is no doubt that the mother must be informed. But in the other cases, in which the heart murmur is the single sign, a remark by the doctor may quite unnecessarily severely upset the mother and secondarily harm the infant, and the whole family. The mothers are often very sensitive during confinement and easily upset even by the slightest suspicion of a defect or illness in their newborn infants. Anxiety about the future of the child frequently affects lactation and causes increasing tension which again may cause adaptation difficulties in the child with accentuated crying and other symptoms of distress. The parents and quite often the physicians too, have a notion that it is dangerous for children with heart trouble to cry, and this again may form a vicious circle. The other members of the family also suffer from the unsatisfactory relations between the mother and her newborn infant.

The author has again and again seen situations with similar reactions that were quite unnecessary because the heart murmurs later proved to be insignificant. He considers it of importance to find a line of action that does not make the physician guilty either of lack of concern for the mother and the newborn infant or of "overdiagnosing".

In the literature only few investigations on the prognosis of the systolic murmurs in newborns are found. The results are not quite consistent and they are rarely discussed from the aspect just mentioned.

In her book on congenital heart diseases, TAUSSIG (1947) warns against overestimating the significance of heart murmurs in the newborn but gives no further details. LYON *et al.* (1940) found that among 7673 newborn infants examined during the first week of life and surviving the neonatal period, 1.9 % had systolic murmurs. No diastolic murmurs were heard. Sex, month of birth, and weight at birth had no bearing on the frequency of heart murmurs, while the frequency seemed to be higher in Negro infants than in white ones. Ninety-two infants, i.e. approximately two thirds of the heart murmur cases, could be followed until the age of one year. In 71 cases the murmurs had disappeared and the infants were considered free from heart disease. Four had died; 2 of them were examined post mortem and found to have congenital heart disease. Fourteen had persistent murmurs, 2 had inconstant ones, and 1 had ectopic beats.

TAYLOR (1953) found that among 1133 newborn infants, who had survived the neonatal period and who were examined more than twice during the first 10 days of life, 4.8 per cent had heart murmurs, all of them systolic. All cases were examined by him. In 12 cases, the murmur persisted during the whole neonatal period, while in the others it was as a rule heard during the first days and then disappeared. Birth weight or sex did not have any bearing on the frequency in this study either. Twenty of the 54 infants were examined at the age of 3, 6, 9, 12, and 24 months. In 14 cases, the heart findings became normal. In 10 of them the murmur had disappeared before the 10th day, in 3, at the age of 3 months, and in one, at the age of 12 months. Two died of congenital heart disease and one of another disorder. Three cases with persistent heart murmurs were considered to have heart disease. In addition, there were 2 infants without heart murmurs who died of heart disease before the age of 2 months.

The most comprehensive investigation on the subject has been recently published by RICHARDS *et al.* (1955). They studied 5964 pregnant women at a maternity welfare centre in New York in order to find out, in the first place how different factors during pregnancy affected the type of congenital malformations and their frequency. There were 5017 full term living infants and 364 immatures. The infants were examined during the first week of life and at the age of 6 and 12 months by the same examiners. Some premature infants could not be examined for the first time until after the first week. For this reason, among others, these infants were treated as a special group.

Among the full term infants who survived the neonatal period, 1.7 per cent had heart murmurs at the first examination. All the murmurs heard were systolic. In this investigation, too, like in that by LYON *et al.*, the Negro infants seemed to have a frequency of murmurs somewhat higher than the white ones; 2.1 and 1.4 per cent respectively. Sixty-nine per cent of the 84 infants had no heart murmurs at the later examinations, while in 17 per cent the murmur was again heard either at the examination at 6 months or at 12 months. Two infants among the 84 died before the age of 6 months, one of them of heart disease. Eighteen infants were examined by X-ray and ECG; 10 of them had heart murmurs at all examinations. Seven of these 10 and one of the other 8 were considered to have heart diseases. In 169 cases heart murmurs were heard for the first time at the age of 6 months and in 100 cases at 12 months. Twelve and 4 cases, respectively, were considered to have heart disease. In two thirds of the group of 169, no heart murmurs were heard at the age of 12 months. Totally, the frequency of heart murmurs during the first year of life was 7.0 per cent. Congenital heart disease was diagnosed in 0.5 per cent of the infants; less than half of these cases (9 of 25) had had heart murmurs during the neonatal period!

Among the premature infants heart murmurs were heard in 2.2 per cent at the first examination (at the age of one to 60 days), the total figure of the first year of life being 9.9 per cent. In this category, however, quite a number of patients failed to come to a later examination. Only in the group with the birth weight varying from 500 to 1500 grams the percentage of murmur (totally 22 per cent) was higher than in the group of full term infants, but the material is too small to allow definite conclusions.

An interesting estimation of the risks of congenital heart disease is made from the above results. In cases where heart murmurs are heard during the neonatal period the risk is 1 : 12. If the murmur is still heard at the age of 6 months, it increases being 1 : 7, and at 12 months it is 3 : 5.

The above studies show clearly that so many different factors are to be taken into account in the evaluation of the results, that an investigation seems hazardous even if prepared in detail and with auscultations performed by one and the same examiner. The author's investigations on the subject, which were carried out before the two last mentioned studies were published, are therefore unpretentious and aim only to give a view on the conditions at a Swedish maternity clinic, where every newborn infant is examined by a pediatrician during the first week of life.

The Author's Material

The material has been collected from the hospital records of the maternity clinic of Uppsala during the 5-year period 1948–1952.[1] Unfortunately there have been several examiners and the date of the first examination varies between the first and the sixth day after birth. On the credit side, however, is the fact that the development of all of the infants has been followed in a satisfactory way at least until the age of one year. This has been possible by examination of the records of Childrens' Welfare Centres, hospitals, and private practitioners. This investigation might thus be of interest not only to the pediatric consultants of the maternity clinics but also to all physicians who are concerned with the prophylactic aspects of infant's welfare work. In Sweden nearly all infants are born at maternity clinics. The Swedish material is therefore less selected than that of the above investigations.

The total material consisted of 11,645 live newborns (cf. Table 1). In this total number, there were 58 cases with heart murmurs, all of them systolic, i.e. 0.5 per cent. Two cases with cyanosis and other signs of congenital heart disease but without heart murmurs during the neonatal period have been included. There are obvious variations in frequency from one year

[1] Prof. JOHN NAESLUND, M.D., head of the Obstetrical Department, kindly put the records at my disposal.

to another. The highest figure of congenital heart disease is found in 1952, following a year of wide spread rubella epidemics, but due to the limited material no definite conclusions are warranted.

Results of Follow-up

The development of all the 58 infants has, as mentioned above, been followed at least until the age of one year. The results are tabulated in Table 1.

Sixteen of the children died during the observation period; eight of these died during the first 2 months, and an additional four during the first year of life. Two of the 16 dead infants were immatures and one a mongolian idiot. Unmistakable heart disease was the cause of death in all cases, in 14 of which it was proved on postmortem examination. All but 2 had inoperable lesions. One of the 2 cases had a tetralogy of Fallot with a nearly atretic pulmonary artery and a markedly overriding aorta, and the other an unusually wide ductus arteriosus and signs of pulmonary hypertension. Both died at the age of 4 months.

In 28 infants, i.e. in nearly half of the whole group, the heart murmur disappeared during the first year of life. Fourteen infants in this group were examined already at the age of 6 weeks and in only one was a murmur still heard. At the age of 3 months only one of the group of 28 had murmur which had disappeared before the age of 11 months. Nine infants of the 28 were also examined by X-ray and ECG; all findings were normal. One immature infant belonged to this group but there were no cases with other

TABLE 1

Year	Live born infants	Murmur during first week	%	No murmur at 3 months	Dead (with heart disease)	Functional murmur	Cong. heart disease
1948	2,606	11	0.4	4	4	1	2
1949	2,445	8	0.3	3	3	0	2
1950	2,378	18	0.8	14	2	0	2
1951	2,108	7	0.3	2	3	1	1
1952	2,108	14	0.7	5	4	1	4
Total	11,645	58	0,5	28[1]	16[2]	3	11[3]

[1] In 1 case the murmur disappeared between 3 and 11 months.

[2] 9 with cyanosis.

[3] 2 with cyanosis.

malformations. It would of course have been of interest to reexamine all the infants. For psychological reasons, however, it was considered unwise.

Heart murmurs persisted in 14 cases. Three of them were interpreted as being functional. On physical examination 4 appeared to be of organic origin, but the ECG and the X-ray picture have been normal up to the present day. Seven cases had unmistakable heart lesions, 2 of them with cyanosis, one since birth. One of the 7 was a mongolian idiot with split palate and upper lip.

The investigation did not show any differences on incidence by sex. Of the 58 living newborn infants, 3 were immature, which is approximately the incidence (about 5 per cent) in the general population.

Conclusions and Comments

A great number of infants with heart murmurs audible during the newborn period will never present signs of organic heart disease. In the author's series 27 out of 58 infants lost their murmurs before the age of 3 months and 1 more infant before 11 months of age. None of these children manifested other signs of heart disease. In an additional 3 children the systolic murmur remained after 1 year of age but was obviously functional in origin. Thus in 31 out of 58 infants, i.e. in more than half of the cases, the systolic murmur heard in the new-born period was not a sign of heart disease.

Of the remaining 27 children, 16 died before the age of 2 years with signs of serious heart disease. All of these 16 children had presented other evident signs of heart disease in addition to the murmurs already in the new-born period: cyanosis (9 cases), dyspnea, feeding troubles and slow weight gain. Of the 11 infants with heart disease who are still alive, 7 are obvious cases, 2 of them with cyanosis.

Beside the cases of heart disease mentioned above, there were others in whom no murmur was heard during the neonatal period. On later examination, the author found undisputable congenital heart disease in 7 infants who, according to the records, had no systolic murmurs during the neonatal period. In addition, there are probably some more cases that remain undiscovered or that have been re-examined elsewhere.

What practical conclusions can be drawn from these observations? The cases showing other signs of heart disease during the neonatal period should undergo a closer examination already at this early stage and the mother should, of course, be informed about the condition. In the author's opinion it will save the parents unnecessary anxiety if information about the presence of a systolic murmur in a newborn infant is withheld until the age of 3 months. During these months the murmurs have disappeared in most

cases (27 of 41) and in the remaining ones no valuable time has been wasted. This line of action is possible only on condition that a later examination is definitely carried out. Therefore it is necessary that the Children's Welfare Centre is informed about the murmur and about the mother's ignorance of it. After the lapse of 3 months, the murmur is of greater diagnostic value and the mother is, as a rule, better balanced, which will make a discussion on the matter easier. If, however, the later examination is not granted it seems wiser to inform the mother at once, bringing all possible optimism into the discussion.

Summary

After a short review of the literature concerning murmurs during the neonatal period the author presents his own material of 11,645 consecutive newborn children of which 58 (0.5 per cent) had murmurs (all systolic) when newborn. In 28 cases the murmur disappeared during the first year of life, in 27 of them before the age of three months. Of the others, 27 had congenital heart disease and 3 functional murmurs. Sixteen of the 27 infants with heart disease died during the first two years of life, and all of them also had other signs of heart disease. The author concludes that if the mothers of the newborn infants with murmurs but without other signs of heart disease are to be informed about the murmur, all possible optimism should be brought into the discussion.

Fréquence et signification des souffles cardiaques chez le nouveau-né.

Parmi 11 645 nouveaux-nés examinés, 58 présentaient des souffles systoliques dès la naissance. Dans 28 cas, le souffle a disparu au cours de la première année, et même 27 fois avant trois mois. Chez les autres enfants, on a noté 27 cardiopathies congénitales, et trois souffles dits fonctionnels. Des 27 enfants porteurs de cardiopathies, 16 sont morts au cours des deux premières années. Tous avaient d'autres signes de leur affection cardiaque. L'auteur conclut que s'il est nécessaire d'informer la mère de l'existence d'un souffle chez son enfant, l'absence d'autres signes de cardiopathie doit tempérer cet avertissement du plus grand optimisme.

Das Vorkommen und die Bedeutung von Herzgeräuschen bei Neugeborenen.

Von 11 645 fortlaufend geborenen Kindern hatten 58 (0.5 %) als Neugeborene systolische Geräusche. In 28 Fällen verschwand das Geräusch während des ersten Lebensjahres, in 27 von ihnen vor dem Alter von drei Monaten. Von den anderen hatten 27 angeborene Herzfehler und 3 funktionelle Herzgeräusche. 16 von den 27 Kindern mit Herzfehlern starben während der ersten beiden Lebensjahren und alle von ihnen hatten weitere Zeichen eines Herzfehlers. Der Autor kommt zu der Schlussfolgerung, dass, wenn die Mütter der Neugeborenen mit Geräuschen, aber ohne zusätzliche Zeichen eines Herzfehlers, über das Geräusch informiert werden, dies mit möglichst optimistischer Einstellung geschehen sollte.

Incidencia y significación de soplos cardíacos en el recién nacido.

De una serie de 11 645 recien nacidos consecutivos, 58 (0.5%) presentaron soplos sistólicos en el período neonatal. En 28 casos el soplo desapareció durante el primer año;

en 27 de ellos antes de los 3 meses. Del grupo restante, 27 mostraron tener cardiopatía congénita y 3 soplos funcionales. 16 del grupo con cardiopatía congénita murieron durante los primeros dos años de vida, todos ellos presentaban otros signos concomitantes de su afección. El autor concluye que si las madres de recién nacidos con soplos pero sin otros signos de afección cardíaca deben ser informadas sobre la significación del soplo, debe mostrarse gran optimismo en la discusión.

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On the Effectiveness of Our Pancreatic Enzyme Preparations

A Study of Fat and Protein Absorption and of the Total Amount of Faeces

by S. BORUP JENSEN and M. SCHNEIDELBACH

Introduction

Pancreatic enzyme has gained increasing ground in the treatment of children with various forms of congenital cystic fibrosis of the pancreas (c.c.f.p.). As early as 1904, BRAMWELL (7) reported the case of a boy with congenital pancreatic steatorrhoea whose stools were trypsin negative and contained much undigested fat. He obtained satisfactory improvement during treatment with pancreatic extract.

It was not until the appearance of ANDERSEN's classic paper on c.c.f.p. (1938) (1) that more systematic studies were conducted on the efficacy of pancreatic enzyme preparations. In a 3-month-old baby ANDERSEN (2) found that the fat percentage of the dry material in the faeces fell from 60 to 45 % (hydrolysis increased from 60–70 to 90 %) upon administration of 1 g of pancreatin powder in each bottle. A similar favourable effect of pancreatic enzyme preparations on the fat content in the stools has been obtained by a number of other workers (e.g. 14 and 15). Moreover, the nitrogen excretion has been found to decrease. Thus, SHOHL (22, 23) reported that on a low fatty diet the nitrogen absorption rose from 50 to 71–83 % upon administration of pancreatin. Lastly, several authors (e.g. ANDERSEN (4) and SHOHL (22)) have found that upon administration of pancreatin the amount of the stools decreases, though not to normal.

A few, however, think that the value of pancreatic preparations is doubtful owing to variations in their potency, to the relatively slight improvement of absorption, and decreased appetite (13, 16, 19).

Authors' Investigations

The patient with c.c.f.p. to be reported below had only slight and transitory pulmonary lesions and was in such good general condition that various pancreatic enzyme preparations were tested on him.

Case Report.—A boy, $2\,^3/_4$ years when last discharged. He was the youngest of 4 siblings, born at term. Uncomplicated delivery. No abnormality at birth: weight 3500 g, length 52 cm. At the age of 10 days, it was observed that he did not gain weight and

that the stools became greenish, frequent, and slimy. He became restless, and his weight fluctuated. Admitted to the Pediatric Department of the Sundby Hospital from Oct. 11, 1951 to July 19, 1952 and from Aug. 3, 1952 to Jan. 18, 1953 for observation for congenital cystic fibrosis of the pancreas. Several attempts at obtaining a sample of duodenal juice failed. For the third time, he entered the department on May 27, 1953 and stayed here until May 21, 1954. This time, a sample of duodenal juice was obtained, on Oct. 31, 1953. It consisted of about 1 ml of a tenacious secretion, pH 4 (gastric juice pH 1) with no tryptic activity. This confirmed the diagnosis of congenital cystic fibrosis of the pancreas. During the stay in hospital the patient had some cough, and in January 1954 chest radiography revealed right-sided interlobar pleurisy which, however, soon cleared.

Treatment: Ordinary diet according to age, water soluble vitamins, iron, and various pancreatic enzyme preparations to be dealt with in more detail.

Special tests: During the last stay in hospital, the patient was examined clinically and biochemically during treatment with various pancreatic enzyme preparations as well as during periods without treatment. He received an ordinary diet according to his age, usually the same from one period to another, the fat and protein contents calculated according to a dietary table, averaging 33.9 and 32.6 g per day respectively. The individual experimental periods extended over 3 days, interrupted by the administration of carmine tablets as a marker, there being at least one week between the periods. During the experiments, which were not always carried out in the same order, the following factors were controlled: Fat and protein absorption, trypsin content and total amount of faeces, body weight, appearance and odour of faeces, glucose tolerance curve, mental condition, general health, and circumference of abdomen. The fat analyses were carried out according to the Schmid-Bondzynski-Ratzlaff method, and protein was analysed by the method of Kjeldahl.

The preparations were as follows: (1) *Pancreatin RMC* (1 g = 70,000 trypsin units, 130 amylase units, 35 lipase units), (2) *Pancreon tablets* (Rhenania) (1 tablet = 28 trypsin units, 18 amylase units, 5 lipase units), (3) *Zymopan tablets MCO* (content per tablet unknown). The preparations were administered in the maximum doses recommended by the manufacturers, i.e. Pancreatin RMC 10 ml (3 g) × 3 (owing to the ease of dosing this granulated substance, ml are used instead of g), Pancreon tablets 3 × 3, and Zymopan tablets 3 × 3.

Results

During the periods without administration of pancreatic enzyme the stools were large, averaging 143–172 g daily. They were formed, pale, smelling of cheese, and trypsin negative. The glucose tolerance curve was flattened (maximum 115 mg %), not increased in breadth. The boy was peevish and irritable.

During the periods with Pancreatin RMC the stools were entirely normal with regard to consistency, odour, and colour. Their bulk was far less, averaging 64–113 g, and the trypsin reaction was positive. The glucose tolerance curve was, if anything, unchanged (maximum 125 mg %), and the boy was in much better spirits and more sociable.

TABLE 1

Treatment	No specific therapy			Pancreatin RMC				Pancreon			Zymopan		
Dates of 3 day period	2–5/11 1953	23–26/11 1953	13–16/1 1954	26–29/9 1953	20–23/10 1953	13–16/12 1953	19–22/2 1954	2–5/12 1953	8–11/2 1954	19–22/3 1954	15–18/11 1953	26–29/1 1954	29/3–1/4 1954
Fat absorption in %	63,6	51,7	55,3	84,8	86,2	84,7	79,8	83,8	69,6	75,8	64,8	53,1	62,6
Protein absorpt. in %		39,9	48,3		85,8	71,4	77,4	74,1	67,1	71,1	63,0	48,6	53,8
Trypsin react of stools	—	—	—	+	+	+	+	+	+	+	—	—	—
Amount of faeces during the 3 days (g)	430	515	465	202	245	340	315	350	400	314	377	450	360
Body weight (g)	12,270	12,280	13,000	9,850	12,550	12,720	13,720	12,350	13,970	14,000	12,300	13,200	13,650
Water content of faeces in %	76,2	74,2	70,8	77,7	78,7	76,6	78,7	78,7	77,6	74,8	74,4	66,4	72,8
Dry substance of faeces in %	23,8	25,8	29,2	22,3	21,3	23,4	21,3	21,3	22,4	25,2	25,6	33,6	27,2
Total fat in native faeces in %	8,2	9,6	9,6	7,1	4,4	4,8	6,5	5,9	9,0	7,7	8,4	12,1	9,0
% of dry substance in faeces: Total fat	34,4	37,2	32,9	31,8	20,6	20,6	30,5	27,6	40,2	30,6	32,8	36,0	33,1
Neutral fat	14,7	14,3	24,3	10,7	7,0	10,7	20,2	13,1	16,1	16,3	16,4	15,5	16,9
Free fatty acids	14,7	18,6	6,5	6,3	7,0	4,7	8,5	7,0	8,1	5,2	12,9	8,6	12,5
Saponified fatty acids	5,0	4,3	2,1	14,8	6,6	5,1	1,8	7,5	16,1	9,1	3,5	11,9	3,7
Total protein		34,5	38,7		33,3	33,7	32,4	34,7	33,5	37,3	35,9	38,9	43,8
Total protein in native faeces in %		8,9	11,3		7,1	7,9	6,9	7,4	7,5	9,4	9,2	13,1	11,9

During administration of Pancreon the stools were larger than during Pancreatin RMC, averaging 105–133 g daily; they were fatty and foul-smelling, but trypsin positive. The glucose tolerance curve was almost normal (maximum 165 mg %), and the boy was in a cheerful mood.

During administration of Zymopan, the stools were larger than during Pancreon therapy, averaging 120–150 g daily, looser, and foul-smelling. The glucose tolerance curve was flattened (maximum 120 mg %). During these periods the boy was irritable, sulky, and cross.

This shows that without specific therapy the absorption of fat and protein was greatly reduced, being 52–64 % and 40–48 % respectively. These values are in accord with most previous findings, the absorption of fat and protein on ordinary diet in c.c.f.p. being reported to range from 40 to 60 % (18, 22, 23), although variations to both sides are marked. It is worth mentioning that, according to most authors, the normal absorption of fat and protein at our patient's age is 95 % or more. At any rate it should be 90 % or more (21, 22).

During treatment with *Pancreatin RMC* there was a very good increase in the absorption values to almost normal levels, 80–86 % and 71–86 % respectively. With *Pancreon* there was a good but less marked increase, to 70–84 % and 67–74 % respectively, whereas with *Zymopan* there was practically no increase, the values being 53–65 % and 49–63 % respectively. Despite the variations within each therapeutic group, the differences from group to group are significant. In addition to the usual experimental errors in balance studies (errors of diet, errors of analysing the faeces, the use of tables instead of chemical analysis of the food etc.), these variations are presumably due also to the influence of other enzyme systems of the gastrointestinal tract as well as to alterations in the state of the diet (degree of emulsion etc.) although it was kept as uniform as possible in all the experimental periods.

It will be seen that without specific therapy as well as during administration of Zymopan, the stools were trypsin negative, whereas they were positive during Pancreatin and Pancreon therapy. The French worker DE MURALT (20) states that pancreas therapy is ineffective, if trypsin is not demonstrable in the stools by the gelatin method. In our patient, the stools became trypsin negative 1 or 2 days after the enzyme preparations were withdrawn.

As mentioned above, the total excretion of faeces was invariably in excess of normal—at the age concerned a maximum of 50–60 g daily (3, 21). The values were highest during periods of no treatment, somewhat lower during Zymopan therapy, still lower during Pancreon therapy, and approaching normal during administration of Pancreatin RMC.

The results of studying the total fat of dried faeces and the individual fractions in per cent of total fat do not give any clue in relation to the normal values, as the latter vary within such wide limits. For instance, the fat content of dried faeces has been reported to vary from 10–80 % (8), although most authors report a maximum of 35 %. The same applies to the fat fractions. Previously most attention was directed to neutral fat as an expression of the effectivity of pancreatic secretion. Numerous investigations have shown, however, that this fraction may be reduced towards or to normal values by bacterial decomposition in the colon as well as by storage at low temperature while the faecal samples are being collected (3). In spite of all this, however, our studies showed that the average percentage of fat in dried faeces as well as the percentage of neutral fat are highest without specific therapy, somewhat lower on Zymopan therapy, still lower on Pancreon therapy, and lowest on Pancreatin therapy, although the differences are slight.

As already stated, the appearance and odour of the stools was typical of the disease in the periods without specific therapy. With Pancreatin, both were normal, with Pancreon the stools were fatty and somewhat foul smelling, and with Zymopan looser and foul-smelling. As in the disease in general, the glucose tolerance curve did not afford any characteristic data.

During all the experimental periods the general health was good, but there is no doubt that clinically the boy was feeling best during administration of Pancreatin. He did not vomit at any time, and the circumference of the abdomen remained constant at about 52 cm. The appetite was poor in one of the periods without specific therapy, but otherwise good, also during treatment with the various pancreatic enzyme preparations. Fluctuations in body weight bore no definite relation to the different preparations, but the mental condition was favourably influenced by two of the preparations.

As apparent from what has been stated above, the dosage was not calculated according to units, partly because the standardization of the various preparations is performed under different conditions and partly because the effect *in vitro* need not represent the clinical effectivity (12). It has been demonstrated by GAD that various inactive substances may reduce the effectivity *in vitro* (10, 11, 12).

Conclusion

Our studies show that Pancreatin RMC is an extremely effective preparation in the treatment of pancreatic fibrosis in children. Pancreon has a good, but somewhat less marked effect, whereas Zymopan is practically ineffective, as also indicated by the study of BASTRUP-MADSEN & MORTENSEN (6).

Summary

The effectivity of various pancreatic enzyme preparations was tested on a boy, aged $2\frac{3}{4}$ years, with congenital cystic fibrosis of the pancreas. These preparations were Pancreatin RMC, Pancreon tablets (Rhenania), and Zymopan tablets (MCO). During periods with no treatment the absorption of fat and protein was 52–64 % and 40–49 % respectively, and the stools were trypsin negative. During treatment with Pancreatin RMC the fat and protein absorption was 80–86 % and 71–86 % respectively, and the stools were trypsin positive. During treatment with Pancreon the fat and protein absorption was 70–84 % and 64–74 % respectively, and the stools were trypsin positive. During treatment with Zymopan the corresponding values were 60–65 % and 49–63 %, and the stools were trypsin negative.

Sur l'activité de nos préparations d'enzymes pancréatiques.

Comparaison entre trois préparations d'enzymes pancréatiques : l'étude montre que la Pancréatine RMC est une préparation extrêmement active pour le traitement de la fibrose pancréatique de l'enfant. Le Pancréon a un effet certain, mais un peu moins marqué, tandis que le Zymopan est pratiquement inactif, comme l'a aussi prouvé l'étude de Bastrup-Madsen et Mortensen.

Über die Wirksamkeit unserer Pancreasenzympräparate.

Drei Pancreasfermentpräparate sind verglichen worden. Es wurde gezeigt, dass Pancreatin RMC ein höchst wirksames Präparat in der Behandlung von Pancreasfibrose bei Kindern ist. Pancreon hat einen guten, aber einen etwas weniger deutlichen Effekt, während Zymopan praktisch unwirksam ist, wie auch durch die Untersuchung von Bastrup-Madsen und Mortensen gezeigt wurde.

Sobre la efectividad de nuestros preparados de enzima pancreática.

Tres preparados de enzima pancreática fueron comparados. El pancreatín RMC es de gran efectividad en el tratamiento de la fibrosis pancreática en la infancia. El Pancreon tiene un buen efecto aunque menor que el anterior mientras el Zymopan es practicamente inefectivo, dato corroborado por los estudios de Bastrup-Madsen y Mortensen.

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Evidence of the Presence of a Pitressin-like Substance in the Tissue Fluids in Nephrosis

by H. ELLIS C. WILSON and AUDREY MUIRHEAD

The demonstration of anti-diuretic activity in the blood of nephrotics by Barlow and its possible association with pitressin and the urine nephrosis peptide suggested by Arneil and Wilson raises the question as to whether the activity is due to substances of pituitary origin, namely pitressin. Evidence in favour of such a hypothesis would be obtained if the blood and urine of nephrotics were shown to possess pressor activity. Such evidence would be further strengthened if it gave further insight into two of the main manifestations of nephrosis, namely oedema and ascites.

The investigations recorded here support the hypothesis that the tissue fluids and urine of nephrotics contain a substance which has pressor activity and behaves chemically and electrophoretically like pitressin.

Methods

The materials used in these investigations were blood, ascitic fluid and urine from nephrosis cases. Anti-diuretic activity was determined by the rat assay method of Burn. Pressor activity was determined on the rat by Dekanski's method. The essentials of this technique are the direct measurement of blood pressure and the use of dibenamine to exclude any action of the autonomic system. Under those conditions any pressor activity must be due either to pitressin or angiotonin. The use of thioglycollate which destroys pitressin only, enables one to test blood for either of those substances separately. In addition to testing blood and ascitic fluid directly for pressor activity, various chemical and electrophoretic procedures were devised in order to obtain more detailed information about the nature of the substance and above all to compare it with pitressin similarly treated.

Ascitic fluid was extracted by the acid (HCl) acetone method of Barnstein *et al.* This technique was employed by those workers for extracting A.C.T.H. from blood for biological assay. After trying out various methods for extracting both anterior and posterior pituitary glands it was considered that this solvent would extract pitressin. The method consists of adding 2 % HCl in acetone 4 volumes, to one of ascitic fluid. The precipitated proteins are filtered off and pure acetone 4 volumes to one are added to the filtrate. This brings down a precipitate which, like the original ascitic fluid, has

pressor activity. The method was found to be applicable to commercial pitressin. A somewhat similar technique was employed for urine. The urine was dried at low temperature and the residue extracted with glacial acetic acid. The extract was centrifuged and a precipitate obtained on addition of excess ether. The acetone extract of ascitic fluid when run on a chromatograph showed usually one spot in the position of the nephrosis peptide. The urine extract showed in addition a number of amino acids.

Electrophoresis Preparations

Preparations were made by paper electrophoresis for pressor assay. Up to 0.5 ml of an extract which might have pressor activity was pipetted on a line across the short axis of electrophoresis paper 6″ × 14″ after it had been soaked in buffer. The buffers employed were 0.01*M* veronal pH 8.6, 0.02*M* Na_2HPO_4 pH 8.0, and 0.02*M* KH_2PO_4 pH 4.0 approximately. The paper was placed between glass plates and the current passed through for 7 hours (approximately 3 volts per cm) at room temperature. The paper was then dried and cut into 1″ strips parallel to the line of application and marked -1, -2, $+1$ etc., according to which pole positive or negative they migrated. The point of application was taken as the nul point (Fig. 3).

These strips were then seeped off with water and used for pressor assay. Commercial pitressin, human posterior pituitary extract and an extract of urine were prepared electrophoretically and used for assay. In all the assays the total volume injected was 0.6 ml, i.e. 0.4 ml test solution plus 0.2 ml 0.9 % NaCl. As control solution (volume effect V.E.) 0.6 ml 0.9 % NaCl were injected. Each figure represents the results obtained with one rat over an experimental period of 2 to 3 hours.

Experimental Results

Assays of nephrosis plasma and ascitic fluid (Fig. 1) show the pressor response of nephrosis plasma (Case D oedema) before and after treatment with thioglycollate and of ascitic fluid (Case C) similarly treated. The response to 3 m.u. pitressin is also recorded for comparison. As 0.4 ml plasma or fluid was injected in each case the blood would contain approximately 5 m.u. per ml and the ascitic fluid 4 m.u. pitressin per ml. It will be noted that the pressor response disappeared after treatment with thioglycollate; hence this would tend to confirm the presence of pitressin. Fig. 2 shows the response of the plasma from the same case (D) after the oedema had disappeared. The pressor response of an acetone extract of ascitic fluid (Case C) shows that the method extracts some at least of the pressor activity. Fig. 2 also shows the direction of movement of commercial pitressin pH 8.6 when run on electrophoresis paper. The maximum pressor activity is in strip -2, the material hence runs to the negative pole. The pressor activity of commercial pitressin (which has been run by paper chromatography in phenol and the end strip cut out and extracted) is also seen. This strip was shown to have marked antidiuretic activity in the rat (Arneil & Wilson). The movement of pitressin at pH 4.0 was also investigated (Fig. 3). At this pH, the pressor principle moves more quickly to the negative pole, namely -3.

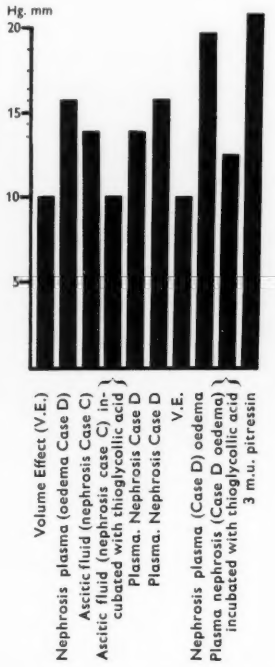

Fig. 1. Pressor response of nephrosis plasma and ascitic fluid.

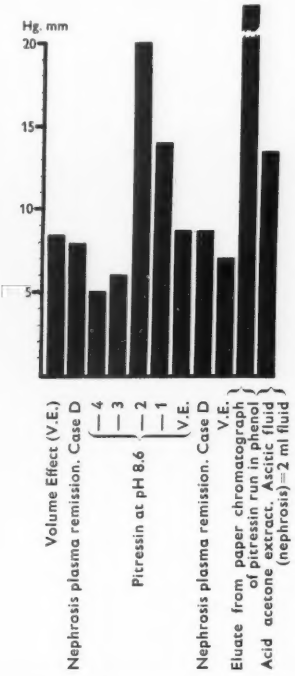

Fig. 2. Pressor responses of electrophoresis of pitressin at pH 8.6 of plasma of nephrosis in remission (without oedema). Acid acetone ext. Nephrosis ascitic fluid. End strip of phenol run of commercial pitressin.

Fig. 4 confirms the pressor response of ascitic fluid and the acetone extracts obtained from it. The response to 4 m.u. pitressin is given and alongside the hypothetical figure for 3 m.u. based on the 2 and 4 m.u. test. The response of 0.4 ml ascitic fluid is approximately equal to that of 3 m.u. pitressin, a figure obtained by intrapolation. The ascitic fluid would therefore contain about 7 m.u. per ml or 7000 m.u. pitressin per litre; 1500 ml fluid would have the same potency as one 10 unit (10,000 m.u.) ampoule. Judging by the rate at which pressor activity disappeared merely on incubation of the fluid at 37°C, even without thioglycollate, it is likely that the amount of pressor substance was much higher while this fluid was gathering in the abdomen. The response of the acetone extract of ascitic fluid merits attention. This extract does not usually dissolve easily in water. The solution was therefore centrifuged and the supernatant fluid decanted off. The small precipitate was washed and

re-suspended in water. Both fractions, namely the soluble part of the acetone extract and the undissolved portion were injected. A pressor response was obtained in each case (Fig. 4). This might indicate either that there are two different pressor substances or that the pressor substance or pitressin is present in more than one molecular form or that it is partially adsorbed on to the precipitate. Li has shown that A.C.T.H. can be obtained in both large and small molecular forms (peptide) from the anterior pituitary gland. Van Dyke *et al.* have prepared active material from posterior glands some of which had a M.W. of 30,000 and some was diffusible. Stehle holds that "one can say with some assurance that the hormones leave the gland as separate substances". Ralli *et al.* have shown that the anti-diuretic activity of urine is present in a dialysable and a non-dialysable form.

Further evidence in favour of the hypothesis that the pressor substance in the tissue fluids of nephrotics is pitressin would be obtained if it could be shown by paper electrophoresis that this pressor substance moved in the same direction as commercial pitressin. For this purpose the acetic acid extracts of urine were run by electrophoresis and the different strips assayed for pressor activity. At pH 8.0 the pressor activity was found in strips -1, and -2 (Fig. 5) exactly the same as with commercial pitressin (Fig. 2). A variation was found with another nephrotic urine run at pH 4.0. Maximum pressor activity was found in strip -2 but there was also a peak at -5 and some activity in $+1$ (Fig. 6). The pattern of a water extract of human (adult) posterior pituitary at pH 4.0 shows maximum activity at -2 (Fig. 7). The results obtained by electrophoresis show then that there is a pressor substance in urine which migrates to the negative pole at much the same speed as the pressor substance obtained from commercial pituitary and an extract of the human posterior lobe. The two peaks obtained with one urine run at pH 4.0 may be due to the presence of the pitressin in two or more molecular forms with different mobilities.

The Significance of Pitressin in Nephrosis

The presence of antidiuretic activity in the blood (Barlow) and urine (Robinson & Farr) of nephrotics has already been shown and the results recorded here show that pitressin or a substance closely allied to it chemically and biologically is also present in some of the body fluids in nephrosis. The presence of substances of different origin but similar activity can not yet be excluded. The problem is, what is the significance of substances having antidiuretic and pressor activity in the etiology of any of the symptoms of nephrosis. It is logical to attribute the oedema and ascites primarily to pitressin? It is more probable however that the fluid retention is initiated by

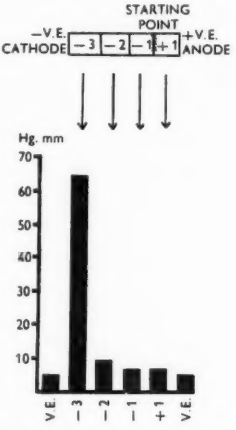

Fig. 3. Pressor responses of electrophoresis of pitressin at pH 4.0.

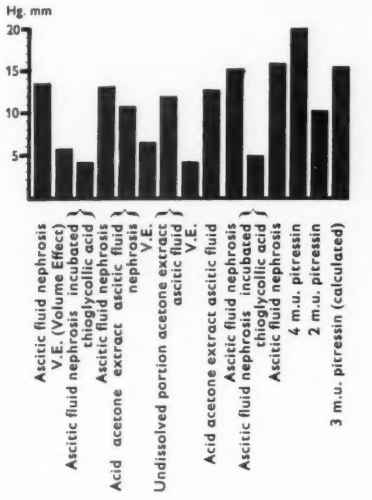

Fig. 4. Pressor responses of nephrosis ascitic fluid before and after incubation with thioglycollate and of acid acetone extracts of ascitic fluid.

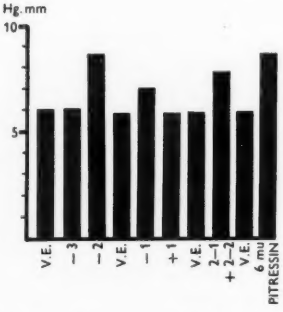

Fig. 5. Pressor responses of electrophoresis of acetic acid extract of urine at pH 8.0.

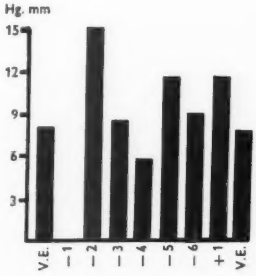

Fig. 6. Pressor responses of electrophoresis of acetic acid extract nephrosis urine at pH 4.0.

a primary salt retention. It is well established that there is salt retention in nephrosis and indeed one of the methods of treatment consists in giving a salt-free diet. By means of radioactive tracers it has been shown that the sodium turnover in nephrosis is very much slower than normal (Burch *et al.*). Verney has shown that one effective stimulus to increased pitressin output

is excitation of osmoreceptors by hypertonic solutions. In the case with ascites recorded here the chloride content of the ascitic fluid varied in different withdrawals from 720 to 817.8 mg % NaCl or about 15 to 20 m.eq. above the normal for extra-cellular fluid. A feasible explanation for the oedema in nephrosis would then be primary salt retention followed by an increased secretion of pitressin.

The Significance of Nephrosis Peptide

A note on the peptides of blood and urine will be published elsewhere. There can be no question that pitressin and pressor and antidiuretic activity are all associated and take up a position by paper chromatography similar to the nephrosis peptide. It can also be said with assurance that peptides can be obtained from other sources without any antidiuretic or pressor activity. Nevertheless peptides can be prepared from urine by various methods which, when run by chromatography, take up the characteristic position of the nephrosis peptide. In addition, when run by electrophoresis and stained by ninhydrin these peptides migrate to strips -1, and -2, positions corresponding to where pressor activity was found when a urine extract and commercial pitressin were similarly treated. Arginine which takes up a position close to the peptide on a paper chromatogram is seen to separate from the peptide when run by paper electrophoresis (Fig. 8).

Fig. 9 shows that the antidiuretic activity of commercial pitressin takes up roughly the same positions, strip -1, and -2, when run on electrophoresis paper. The evidence then shows that urine does contain peptides which could be of pituitary origin.

Conclusion

The presence of a pressor substance has been detected in the blood, ascitic fluid and urine of cases of nephrosis.

The chemical and electrophoretical characters of the substance resemble those of commercial pitressin and human posterior pituitary extract. The detection by paper chromatography of a nephrosis peptide in tissue fluids is not necessarily an indication of the presence of pitressin or products of the anterior or posterior lobe of the pituitary gland.

Peptides can be obtained from body fluids which when examined by electrophoresis and paper chromatography resemble those prepared from commercial and human pituitary extracts.

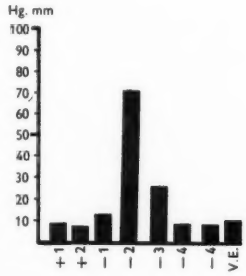

Fig. 7. Pressor responses of electrophoresis of extract of human posterior pituitary gland at pH 4.0.

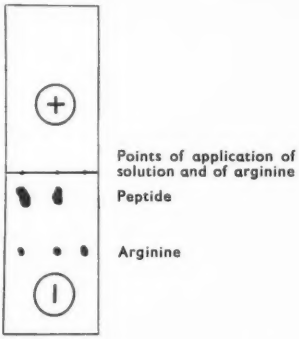

Fig. 8. Movement of peptides and arginine by paper electrophoresis.

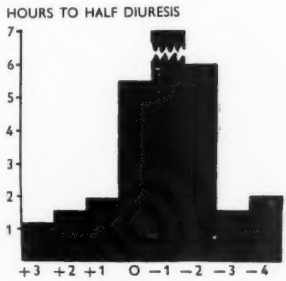

Fig. 9. Antidiuretic responses of electrophoresis eluates of pitressin.

Preuves de la présence d'une substance analogue à la Pitressine dans les liquides tissulaires des néphrotiques.

Une substance à effets presseurs a été mise en évidence dans le sang, le liquide ascitique et l'urine de néphrotiques. Les caractères chimique et électrophorétique de cette substance sont analogues à ceux de la Pitressine du commerce ou d'extraits de la partie postérieure de la glande pituitaire humaine. La mise en évidence par chromatographie sur papier d'un peptide de néphrose dans les liquides tissulaires n'indique pas obligatoirement l'existence de Pitressine ou d'hormones de la partie antérieure ou postérieure de la glande pituitaire. On peut mettre en évidence dans les liquides du corps humain des peptides, qui lorsqu'ils sont examinés par électrophorèse ou par chromatographie sur papier ressemblent à ceux issus d'extraits humain ou commercial de glande pituitaire.

Der Nachweis einer Pitressin-ähnlichen Substanz in der Gewebeflüssigkeit bei Nephrose.

Eine depressorische Substanz ist bei Fällen mit Nephrose im Blut, Ascites und Urin entdeckt worden. Der chemische und elektrophoretische Charakter der Substanz ähnelt dem des käuflichen Pitressins und dem Extrakt des menschlichen Hypophy-

senhinterlappens. Der papierchromatographische Nachweis eines Nephrose-Peptids in der Gewebeflüssigkeit ist nicht unbedingt ein Hinweis für die Gegenwart von Pitresin oder Produkten des Vorder- oder Hinterlappens der Hypophyse. Peptide können aus Körperflüssigkeiten gewonnen werden, die bei Untersuchung durch Elektrophorese und Papierchromatographie den kommerziellen und menschlichen Hypophysenextrakten gleichen.

Evidencia de una sustancia similar a la pitresina en los fluídos orgánicos de los nefróticos.

Una sustancia presora ha sido detectada en la sangre, líquido ascítico y orina de pacientes nefróticos. Los caracteres químicos y electroforéticos de esta sustancia imitan los del pitresín comercial y extractos de posterohipófisis humana. La detección, por cromatografía en papel de un péptido en los fluídos orgánicos, no indica necesariamente la presencia de pitresin o productos de antero o pósterohipófisis. Algunos péptidos pueden ser extraídos de dichos fluídos los cuales al ser examinados por cromatografía y electroforesis semejan a los preparados comerciales o extractos pituitarios.

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From the Children's Hospital, Linköping, Sweden

Children Chronically Diseased

by GILLIS HERLITZ and BJÖRN REDIN

To give a precise definition of what the term "chronic disease" implies is no easy task where adults are concerned; it is still more difficult when referring to children. The latter, as a rule, are capable of recuperating—even from longstanding and serious organic disease—to a far greater extent than adult persons. It is therefore in no way remarkable that the term "chronically diseased" is applied much more sparingly to children than to adults.

None the less, there are many morbid conditions of infancy and childhood that unhesitatingly are named chronic. Examples are diabetes, mental subnormality, inoperable congenital heart defects, and, in most instances, cerebral palsy. In other cases children suffer from diseases which, without being chronic in the sense that they necessarily will last for life, yet despite adequate treatment for many years are apt to produce continuous or intermittent trouble and/or carry an obvious risk of future incapacitation. These children are generally in need of unceasing medical supervision, and frequently they require special measures of social aid and rehabilitation. Owing to the difficulties arising when such patients are treated at home, hospital or institutional treatment for shorter or longer periods is necessary in a good many of these cases. In practice, it would thus seem appropriate to regard these children also as chronically sick. Examples of such morbid conditions are epilepsy, grave asthma, "chronic" rheumatoid arthritis, and tuberculosis.

It is impossible, naturally, to achieve any definite and invariably correct delimitation between, on the one hand, the types of disease considered above and, on the other, those to be classed as acute or subacute. Of transitional forms there are many, and the variation in the course of one and the same disease in different children is practically boundless. However, notwithstanding the evident difficulties of classification, it may sometimes be worth while to try and set the chronically sick children apart from other young patients. When planning a programme for the care of sick children in a given district it is essential to realize the special, medical as well as social, problems posed by those children that are completely or partially incapacitated by longstanding sickness.

In endeavouring an over-all survey of the chronically sick children living within a fairly large area we have applied the criteria of chronic disease as stated in the above paragraphs. Moreover, for every separate disease involving some doubt, in the following the reasons for classing a case as chronic will be given in detail. The investigation was limited to 10 one-year groups, viz. 2–11 years. One half of these groups fall below school age and the other half within school age. As chronically sick infants apparently come under a separate category, *inter alia* because as a rule they require admission to special hospitals, their problems will be dealt with in a separate section.

The area studied, i.e. Östergötland county, is a predominantly rural district in the south of Sweden with a total population of 264,670, of which 40 % are living in towns. The area has only one pediatric hospital, in the records of which practically all the children concerned here will sooner or later appear. In addition, information was procured from all other county hospitals and services treating children (departments of otolaryngology, ophthalmology, orthopedics, poliomyelitis ambulatorium, hearing-aid service, sanatorium and central dispensary for tuberculous diseases, homes for the mentally deficient) and, outside the county, from those institutions and homes for blind, deaf, epileptic, rheumatic, and crippled children admitting patients from the whole country of Sweden. Ultimately, however, the investigation has been based upon data forwarded by the 59 district nurses of the county, who are thoroughly familiar with the child-health conditions existing in their districts of some 4500 persons. As to details of procedure pertaining to the census investigation, reference is made to our preceding papers on cerebral palsy and mental subnormality in children.

The children presenting at the same time two or more of the chronic diseases considered in the present study—which in actual fact occurred only where mental subnormality was one of the components (e.g. mongoloid idiocy with congenital heart defect, cerebral palsy with mental subnormality, epilepsy with mental subnormality)—were classed only under the heading, mental subnormality, which invariably was the most important factor as regards practical points of nursing. Cases of cerebral palsy associated with epilepsy were recorded as cerebral palsy alone. Some of the diseases which actually are chronic in the sense specified above for obvious reasons could not be included in the survey, viz. diseases such as eczema, myopia, psychopathy, mild mental retardation (see below), and chronic otitis not entailing persistent, serious impairment of hearing.

The total series is presented in Table 1, where the various types of disease are arranged in numerical sequence.

Prevalence.—On Dec. 31, 1953, there were in Östergötland county 46,100 children aged 2–11 and fairly evenly distributed among the 10 one-year classes. Accordingly, as computed on the basis of our entire series, the incidence of chronic sickness in children within our county is 12.39 per 1000 children in the age classes in question (boys alone, 14.54, girls, 10.16). For the group of lower-age classes (2–6 years) alone the ratio is 11.09, and for the higher-age classes (7–11 years) it is 13.70.

Age in years	2–3		3–4		4–5		5–6		6–7		7–8		8–9		9–10		10–11		11–12		12–13		Totals		Incidence per 1000		
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	2–6 ♂+♀	7–11 ♂+♀	2–6 ♂+♀	7–11 ♂+♀	2–11 ♂+♀
1. Mental subnormality	12	6	8	6	18	11	21	6	15	11	10	11	27	11	17	16	12	13	17	14	157	105	262	148	4.96	6.43	5.70
2. Epilepsy (cases with cerebral palsy or mental subnormality not included)	2	1			4		3	2	5	1	4	2	3		3	4	4	1	5	4	33	15	48	30	0.78	1.30	1.04
3. Cerebral palsy (mentally subnormal cases not included)	1	2	4	2	4	2	1	3	3	3	2		2	2	2	1	1		2	4	22	19	41	16			0.89
4. Diabetes		2			3	1	4	1	1		4		1	2	2	3	4	4	3	3	22	16	38	26	0.52	1.13	0.83
5. Heart disease (congenital and aquired)	3	3	2		2	2	2	1	1	2	4	2	5	1	2	2	2		1		24	13	37	19			0.80
6. Sequelae of poliomyelit					1	2	2	2	1		7	2	1	3	5	1	3	1	2	1	22	12	34	8	0.35	1.13	0.74
7. Asthma	2	1	4		1	3	1	1	1	2	1	1	4	3	2	1	1		1	1	18	13	31	16			0.67
8. Congenital malformations (not listed elsewhere)	3		2	1		1	1				1				3				1		8	5	13	8	5			0.28
9. Deafness	1				2	1	1		1	2	1	2	1						1		8	5	13	8	5			0.28
10. Endocrine disorders					1		1		1	2					1		1			3	4	7	11	6	5			0.24
11. Organic disease of the nervous system (polio not included)			1		2	1	2								2		2				8	2	10	6	4			0.22
12. Diseases of the bones and joints (tb. not included)			1		1		1		1		1	1	1				2		1		5	4	9	3	6			0.20
13. Blindness		1	2		1		1				2										0	7	7	5	2			0.15
14. External injury (birth trauma not included)	1		1																1	1	3	1	4	2	2			0.09
15. Diseases of the blood					1		1												1		2	1	3	2	1			0.07
16. Diseases of the kidney (congenital malformations not included)												1		1												0.04	
17. Tuberculosis								1											1		1	1	2	1	1			0.04
18. Diseases of the digestive system																					1	1	2	0	2			0.04
19. Various diseases					1					1			1								2	1	3	2	1			0.07
Total	25	16	22	14	39	28	39	17	30	25	33	23	48	23	36	31	33	21	36	31	341	229	570	255	315			12.39

The incidence rates per type of disease, computed for 1000 children aged 2–11, are presented in Table 1. In respect of the four disease groups with markedly higher incidence among older versus younger children, data are given pertaining to the groups, 2–6 and 7–11 years.

Age Distribution.—In our county, the normal population in the age sections here surveyed includes as many individuals in the 5-year group below 7 years as in that above 7 years. The present material discloses an overrepresentation of the latter 5-year group, which includes 55.3 % of the series. This is probably not due to mere chance (difference, 5.26 ± 2.09 %) and applies equally to boys and girls. Nearly exclusively the groups mental subnormality, epilepsy, diabetes, and poliomyelitis are responsible. With rising age the three last disease groups receive contributions in regular succession, and the first group must always be expected to preponderate at higher age, mental subnormality not always being recognized or admitted before school age. The reverse is true in our table of the group Cerebral Palsy. Here the younger children predominate because in them mental subnormality could not be definitely established at so early an age; in so far as mental deficiency sufficiently grave in degree was detected in them, they were automatically referred to the group Mental Subnormality.

Otherwise the age distribution is fairly level in the entire series. The cardiac defects are chiefly congenital and are revealed at an early stage. Asthma will probably set in more frequently in earlier childhood than later on; the equilibrium between the age groups is restored by the recovery of more children in the course of time and the death of a few of them.

Sex Distribution.—The boys predominate in the entire series, i.e. above as well as below the age of 7 and within every disease group *per se*. Possible exceptions are the groups endocrine disorders and blindness, and naturally the small disease groups cannot properly be assessed. No less than three fifth of the material are boys. In our county, the normal distribution for these ages shows only 51 ± 0.24 % boys. The difference is valid statistically (8.82 ± 2.07 % for the total material). The differences being of approximately the same order of magnitude in the age groups above and below 7 years and in all disease groups *per se* where the figures are large enough to allow comparison, the sex difference is rather hard to explain except by assuming a greater general liability to disease of the boys included in the age groups here discussed.

Disease Groups

Mental Subnormality.—This group alone supplies nearly half the material (46 %). A mentally subnormal child here means one who because of general mental retardation is unable to profit from the ordinary tuition given in

Swedish elementary schools or in the special classes of these where a slightly modified tuition more suited to backward children is given. Thus, the border line will be drawn at an intelligence level corresponding to that of about 10–11 years for adults (I.Q. about 65–70). For closer details as to the delimitation of this material and the special problems involved see our preceding paper on mental subnormality in children. As has been mentioned, the group also includes cases of epilepsy and cerebral palsy.

Epilepsy.—The group comprises only such cases of so-called genuine epilepsy where mental subnormality in the above sense or cerebral palsy were absent. We have included those instances in the survey where the duration of sickness was at least 1 year, and where the patient at the time of investigation was still being treated, whether successfully or not. Of the 48 cases included in the group, electroencephalograms were still abnormal in 41. In the remaining 7 data were lacking on this point (3 were inmates of homes for epileptics, and in 4 no EEG had been done).

Cerebral Palsy.—As has been stated above, here only cases were included in which there was no evidence of concurrent mental subnormality. A detailed report on the group Cerebral Palsy has been presented by us in a preceding paper.

Diabetes.—As regards this group, naturally delimitation for purposes of the present study was easier than in the other groups, and special comments are not required.

Heart disease.—In all 37 cases there were, of course, objective signs of cardiac impairment. Twenty-eight patients had appreciable symptoms of their cardiac defects which were noticed by the attendants. In 3 children symptoms of this type were lacking, but they all had congenital defects with dubious prognosis (coarctation of the aorta was present as a component in every one of the three cases). As regards the remaining 6 children, there was some doubt as to the presence of symptoms, but the cardiac changes observed were so grave in nature that the children had to be regarded as virtually suffering from chronic disease (appreciable cardiac enlargement in 4, total block in 1, other electrocardiographic abnormalities in 1). Postcarditic conditions mild or moderate in degree of severity and not giving rise to symptoms, were not included. Among the congenital abnormalities, simple defects of the ventricular septum without symptoms were excluded from the survey, as were the few cases of patent ductus arteriosus without symptoms which so far have not been operated upon in our county. Of the 37 cases comprised in the group 28 are congenital and 4 postcarditic. In the remaining 5 the aetiology is obscure. Of the 28 congenital cases 11 are inoperable, and 6 have been operated upon without subsidence of symptoms; the remaining 11 are possibly operable cases.

Poliomyelitis.—Only those cases are included where the children are markedly incapacitated by their disease, and where the onset of paresis dates back for at least 1 year. Thus, milder residual paresis was excluded. As regards paresis of legs, *inter alia* obvious impairment of the ability to walk was made conditional for inclusion in the survey. Of the 34 children 22 present paresis only of legs, 3 only of arms, and 2 of the trunk only; the remaining 7 present combinations of these types.

Asthma.—In regard of this group the difficulty of deciding whether or not the children were chronically sick, was greatest. Eventually we included only those cases where the symptoms are continual or nearly so, and where more serious attacks occur at least once a month. Another condition was that the duration of sickness was at least 1 year. Accordingly, the cases frequently met with, where attacks moderate in degree occur a couple of times a year in conjunction with upper respiratory infection, are not included.

Congenital Malformation.—A proportion of cases was for practical reasons included under other headings (heart disease, blindness, etc.). Of the remaining 13 cases 9 relate to the urinary tract, and in 4 incapacitating, multiple malformations of other kinds are present. The genito-urinary malformations are either inoperable, or symptoms persist in spite of surgery. All the children have chronic symptoms, viz. mainly from pyuria.

Deafness.—Only those children are included in the material who are incapable, or expected to be incapable, of participating in the ordinary tuition at school owing to their loss of hearing. All of them are either admitted to special schools or deaf-mutism institutions, or expect admission.

Endocrine Disorders.—Of the 11 children, 10 suffer from myxoedema and 1 from hypoparathyroidism. None of the myxoedema patients included in the group are to be classed as mentally subnormal.

Organic Diseases of the Nervous System.—The group comprises 5 cases of progressive muscular dystrophy, 2 of hereditary ataxia, 1 of double athetosis, 1 of amyotonia congenita, and 1 of chronic encephalitis.

Diseases of Bones and Joints.—The group includes 2 cases of fragilitas ossium, 2 of arthrogryphosis, 2 of chronic rheumatoid arthritis, 2 of chondrodystrophia foetalis, and 1 of osteogenesis imperfecta.

Blindness.—To this group those children were referred who are either completely blind or able to see just enough for unaided walking. Three of them have retrolental fibroplasia and another 2 congenital cataracts.

External Injury.—The group includes 3 cases of oesophageal stricture due to a caustic and 1 case of loss of a limb following an accident.

Diseases of the Blood.—Three cases of incapacitating haemorrhagic diathesis.

Diseases of the Kidneys.—Two cases of chronic nephritis.

Tuberculosis.—One case of pulmonary tuberculosis and 1 case of tuberculous coxitis.

Diseases of the Digestive System.—Two cases of ulcerative colitis with a history of several years.

Various Diseases.—One case of calcinosis universalis following dermatomyositis, 1 case of chronic hypersensitivity disease, and 1 case of incapacitating epidermolysis bullosa hereditaria.

Infants

For obvious reasons, the chronic diseases of the first or the first and second years of life must be expected to differ rather markedly from those of later years. A census investigation conducted on the lines specified above and pertaining to children aged 2–11 is scarcely feasible where infants are concerned. Instead, to form an idea of the types and incidence rates of chronic diseases of infancy we have preferred to investigate the records of the last few years at the only department of pediatrics of Östergötland county. Probably all cases of serious, protracted sickness in infants living in this county are investigated and treated in that department. It was thus found that yearly about 20–25 cases of chronic sickness during the first year of life come under our care. As far as possible, the criteria of chronic sickness were made to conform to those adopted for the older children. It stands to reason that in the case of infants the figures must be interpreted with still greater caution. They cannot convey more than a rough impression of the situation. Also, in this group the annual loss of lives is greater than in the others. The diseases in question which predominate in infancy seem to be sequelae of brain damage, cardiac and genito-urinary malformations, disturbances of metabolism, coeliac disease, and fibrosis of the pancreas.

Social, Therapeutic, and Educational Aspects

Sequelae of cerebral damage (mental subnormality, epilepsy, cerebral palsy) which alone are responsible for three fifths of all chronic diseases in children, constitute the most urgent problem. The major proportion of them being due to anomalous circumstances affecting gestation and parturition, the measures to be taken should be directed in the first place towards improvement in prenatal care, obstetric management, and treatment of premature children.

Among the mentally subnormal children in our series at least 40 % are unable to learn how to use the symbols of arithmetic and the spoken sounds (figures and letters). Most of them are in need of institutional care, at least

after having passed through the first few years of life. All the remaining, presumptively "educable" children (60 %) require tuition in special schools after—and quite a few even before—having reached school age. In other words, in our county the community has to arrange such schooling opportunities for at least 0.5 % of all children at school age. As has been mentioned earlier, the special classes of our elementary schools which offer a slightly modified tuition more suited to backward children, are inappropriate for the children included in our group Mental Subnormality.

Of the 48 cases in our series of epileptics 4 are so grave in degree as to require long-term institutional care. In the remaining cases ambulant treatment is possible, and the patients may remain in their homes except for short periods of hospitalization for institution of therapy with new drugs. All of them who have reached school age are able to participate in the tuition offered by elementary schools, though with varying success.

In the group Cerebral Palsy 10 children should be expected to require admission, for shorter or longer periods, to special departments for children with central motor damage. The rest can be treated as ambulant patients with physical, orthopedic, play and occupational therapy etc. which naturally should be done under expert guidance and, in so far as geographic and other circumstances permit, in a central place. In about one fourth special speech training is required. In this group the schooling problems loom large, and for about half the children private education at home or in a day-home for spastics is the only possibility. It stands to reason that as many as possible of the children with cerebral palsy who belong in the group Mental Subnormality also should be afforded the benefit of the treatment and tuition discussed here, viz. in so far as this is within their mental power.

The diabetics who are treated on an ambulatory basis with check-ups at regular intervals, as a rule do not pose larger problems of social care as long as they are at the age of childhood. The children with congenital heart defects who constitute roughly four fifths of our material of cardiac diseases, once having passed through the first few years of life form a selected series of viable malformations. None the less, several of them are rather seriously incapacitated, although only exceptionally to such an extent as to be bedridden and unable to move about. None of the children included in our group need continuous bed-rest or longer periods of hospitalization. Invariably they can be treated at home, and generally they are leading a normal life excepting the restriction of movements enforced by their condition. Their schooling has not been hampered in any case. As in the diabetics, the late prognosis is the most important problem in these children. — Of the acquired cardiac defects, which are comparatively rare in our material, much the same is to be said as of the congenital defects.

The children suffering from sequelae of poliomyelitis, who as a rule have to be under the care of orthopedists and physical-training experts for considerable periods, after the first long-term hospitalization, in the main need ambulatory treatment only. Their schooling, like that of many other children chronically sick, depends on transport facilities, and hence is principally a local problem. In our material education in a home for cripples was necessary in no instance.

The children with asthma in our group are to a large extent in need of hospitalization as emergency cases during their attacks. In the intervals between attacks many of them are very markedly incapacitated in spite of all treatment. As regards these children, it has proved necessary in our part of the country to remove them for longer or shorter periods from the allergen-contaminated surroundings of their homes, not least in order to avoid the impending persistent emphysema. Accordingly the care of the asthmatic children has become a social problem of the first order. With the therapeutic resources at present available, a thoroughly satisfactory management of these cases requires, at least in respect to our county, facilities for removing them for longer or shorter periods from their homes to a suitably placed institution where arrangements can be made for their schooling.

All the deaf and blind children are committed to long-term care in special asylums, in which their entire schooling will also have to take place. The children with endocrine disorders can be treated ambulant, and their education as a rule can be carried out in the ordinary way, although special classes are required for most of the myxoedema cases. In most instances the diseases of the nervous system will incapacitate the children to such a degree that ordinary schooling is exceptional. These children will therefore become inmates of cripple asylums, often for very considerable periods. The same applies to children with multiple malformations. In our material the diseases affecting the skeletal system, and the external injuries, do not implicate such problems of management. On the other hand, the rest—genito-urinary malformations, chronic rheumatoid arthritis, diseases of the blood, kidneys, digestive system, tuberculosis and the diseases listed as "various"—are of such nature as to enforce repeated long-term hospitalization of the children.

As a rule, the chronic diseases of infancy are of such kind, and of such an importance for the general development of the child, that continuous hospitalization in a department of pediatrics is required. Exceptions are principally the cerebral conditions which in a given case can be treated in other institutions or at home.

Conclusion

As in all census investigations, the incidence rates found by us must be regarded as minimum values, the more so since we were rather reticent to assess a child as chronically sick.

The chronic diseases of children call for increased attention on the part of the community. The efforts must be directed towards prevention, early diagnosis, energetic treatment at the correct place, rehabilitation, vocational guidance and training, and, finally, employment of the sick. Particular attention should be paid to the need of emotional adjustment of these children and to the information needed by their parents as to the peculiar position of the patients and their future fate. In addition, the educational problems require careful consideration. The best way to promote the interests of chronically sick children within a given district seems to be the management of their affairs by a team in which the expert knowledge represented by pediatricians, orthopeds, teachers, physiotherapists, occupational therapists, social workers, and vocational advisers is available. Such teams for aiding the spastic children are being formed in several districts of Sweden. It would seem desirable that this team-work be extended to include all children chronically sick, not excepting those mentally subnormal. The essential social problems are the same for all children suffering from chronic disease.

Summary

On the basis of specified criteria we have attempted to carry out an over-all survey of chronically diseased children in a 10-year series of a population of 265,000 in Sweden. The incidence of chronic disease was 12.4 per 1000 children aged 2–11 years. Sixty per cent of the material were boys. The various groups of incapacitating diseases are reviewed and social, therapeutic, and educational problems discussed. The present writers urgently demand increased attention on the part of the community for the chronically sick children and advise a conjoint management of their affairs on a team-work basis within the separate health-service areas of the country.

Les affections chroniques chez l'enfant.

En se basant sur des critères déterminés, les auteurs se sont efforcés de dresser un bilan des affections chroniques de l'enfance en Suède, dans un groupe de 265 000 personnes, et en étudiant une période de dix années. La fréquence a pu être fixée à 12.4 pour mille enfants, âgés de 2 à 11 ans. Soixante pour cent d'entr'eux étaient des garçons. La nature des affections causales est indiquée, et les problèmes sociaux, thérapeutiques et éducatifs qu'ils posent sont passés en revue. Les auteurs sollicitent une attention accrue à l'égard de ce groupe d'enfants atteints d'affections chroniques. La solution des problèmes nécessite la collaboration en équipe des divers services sociaux du pays.

Chronisch kranke Kinder.

Auf der Basis von spezifizierten Kriterien haben die Autoren versucht, sich einen Überblick über chronisch kranke Kinder in einer 10-Jahresgruppe einer Bevölkerung von 265 000 in Schweden zu verschaffen. Das Vorkommen von chronischen Erkrankungen betrug bei Kindern von 2–11 Jahren 12,4 auf 1000. 60 % des Materials waren Knaben. Die verschiedenen Gruppen der die Leistungsfähigkeit herabsetzenden Erkrankungen werden geprüft und soziale, therapeutische und erzieherische Probleme erörtert. Die Autoren fordern dringend eine stärkere Beachtung chronisch kranker Kinder und empfehlen eine gemeinschaftliche Handhabung ihrer Belange auf Team-Work Basis innerhalb der einzelnen Gesundheitsdienstbezirke des Landes.

Niños con enfermedades crónicas.

Sobre las bases de un criterio específico, los autores han intentado llevar a cabo una pesquisa de niños cronicamente enfermos en una serie de 10 años de edad correspondiente a una población sueca de 265 000 habitantes. La incidencia de enfermedades crónicas fué de 12.4 por 1000 niños entre los 2 y los 11 años de edad. 60 por ciento del material eran varones. Se revisan los distintos grupos de enfermedades incapacitantes discutiéndose los problemas sociales, terapéuticos y educacionales. Los autores requieren urgente atencíon, de parte de la comunidad, hacia los niños cronicamente enfermos y aconsejan un manejo conjunto de sus problemas sobre la base de trabajo en equipo entre las areas del servicio de saludad de diferentes partes del país.

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Cortisone Treatment in Vitamin D Intoxication[1]

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Beneficial effects of cortisone in the treatment of sarcoidosis complicated by hypercalcemia have been reported by Dent, Flynn & Nabarro, and by Anderson, Dent, Harper & Philpot. The hypercalcemia in this condition is supposed to be caused by an abnormally high calcium resorption from the intestines occurring at the same time as there is a dissolution of mineral salts from the skeleton, i.e. the sequence is thought to be the same as in vitamin D intoxication (cf. Albright & Reifenstein and Carlsson). In this communication the effect of cortisone in a child with vitamin D intoxication will be reported. During this therapy the serum calcium level was normalized in a short period and concurrently there was a rapid improvement of the patient.

Case Report

A girl, 11 months of age, was admitted to the Pediatric Clinic, Karolinska Sjukhuset, in June 1955 with the diagnosis of vitamin D intoxication. She was breast fed for 6 months and had developed normally until the age of 8 months. There were never any signs of rickets. In December, 1954, when the patient was 5 months old, a daily dose of 90,000 units of vitamin D_2 was prescribed to be administered every other week. Beginning in March, 1955, the same dose was given daily without any interruption and continued for another two months. The total quantity of vitamin D given during these five months has been calculated to be about 8 million units. After three months of high vitamin D administration the child became hypotonic and lost her appetite, and after another two months she developed severe symptoms of vitamin D intoxication.

Physical examination on admission revealed an 11 months old, extremely pale, dehydrated and hypotonic child in poor general condition. The fontanel was not closed and was not bulging. The systolic blood pressure was 60 mm Hg.

Radiological investigation of the skeleton did not reveal any abnormalities. In the electrocardiogram there was a shortened Q–T interval.

Some of the biochemical findings are summarized in Fig. 1 and Table 1. There was a marked hypercalcemia and a marked hypercalcuria. The non-protein nitrogen level was normal. There was a slight acidosis, but the ability of the kidneys to acidify the urine was not impaired, as was demonstrated after an acid load. The electrophoretic pattern of the serum proteins was normal. The daily urine volume was 300–400 ml with a specific gravity of 1.010 or less. There was a slight intermittent albuminuria, but no red cells were found in the urine.

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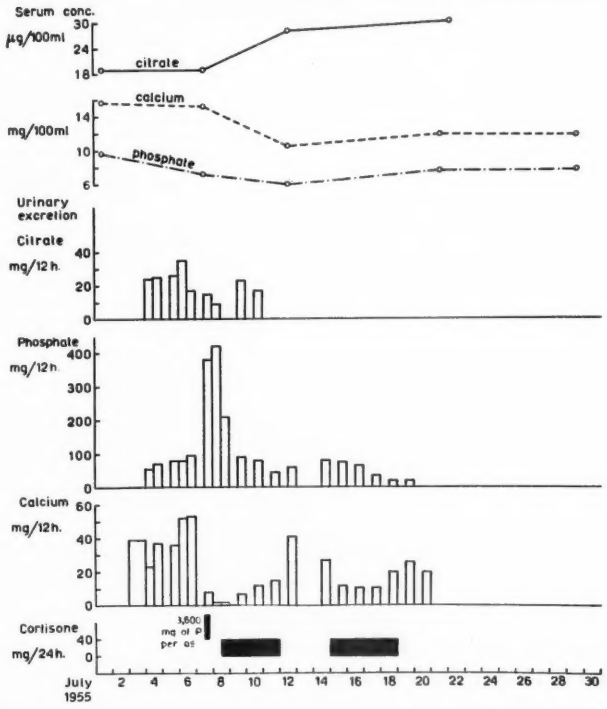

Fig. 1. Metabolic effect of cortisone in vitamin D intoxication. The serum calcium level and the urinary calcium excretion were high before therapy. Cortisone caused a rapid normalization.

TABLE 1

Blood chemistry in the patient with vitamin D intoxication.

	Sodium mEq/l	Potassium mEq/l	Chloride mEq/l	$BHCO_3$ mMol/l	NPN mg/100 ml	Alkaline phosphatase Busch units
1955						
VII, 5			94	18	35	5
VII, 7	139	5.1	102	17.5		
VII, 14				21.6		4.5

One week after admission cortisone treatment was started. The hormone was administered perorally every 6th hour in two different four-day periods with an interval of three days between them. Throughout this period the patient was kept in bed and fed a constant diet containing 700 g of human milk, juice and some vegetables.

Studies of the Effect of Cortisone Treatment

Methods

Urine was collected quantitatively in 12-hour periods, usually only during the night. Urine for the determinations of pH and carbon dioxide combining power was obtained by catheterization and was collected under mineral oil. Citric acid excretion was determined in urine samples collected with toluene as a preservative. For the analytical work ordinary routine methods were applied.

Results

General effect.—After institution of cortisone treatment there was a marked general improvement of the patient. She became alert and active, and anorexia, hypotonicity and the symptoms of dehydration disappeared. This change of her general state coincided with a rapid fall of the serum calcium level.

Calcium metabolism.—As can be seen from Fig. 1 hypercalcemia was marked prior to treatment, the level being stationary between 15 and 16 mg per 100 ml serum. After institution of cortisone therapy a pronounced and rapid fall in serum calcium concentration occurred.

Before treatment there was a marked hypercalcuria, the calcium excretion in the urine varying between 35 and 50 mg per 12 hours, corresponding to 9–13 mg per kg body weight per 24 hours (the normal range being 1.1–4.9 mg per kg body weight per 24 hours, cf. Albritton). The pronounced reduction of the urinary output of calcium just before the first period of cortisone administration might have the following explanation: Eighteen hours before the first period of cortisone treatment, an oral dose of 3600 mg of phosphorus as a sodium–potassium phosphate solution was administered during six hours. Fig. 1 shows that the phosphate excretion in the urine increased four to five times after ingestion of this solution. At the same time there was a marked reduction of calcium excretion in the urine. While the phosphate output successively diminished to values within the same range as those observed before the phosphate load, there was a gradual rise of the urinary calcium excretion which, however, amounted to only about one third of the values previously observed. Since the calcium excretion rose markedly as soon as cortisone was stopped, the depression of the calcium excretion, at least during the last two days of this treatment, seems to be caused by cortisone. This statement is supported by the observation that the calcium excretion also diminished during the second period of cortisone administration. At the end of the last cortisone period there was a slight but insignificant rise of the calcium excretion.

Phosphate metabolism.—Before treatment the serum phosphate level was high but the urinary output of phosphate low, amounting, approximately,

to only one tenth of the amount ingested. These findings seem to indicate a low activity of the parathyroid glands, cf. Albright & Reifenstein. During the second period of cortisone treatment there was a successive decrease of the urinary output of phosphate although the serum phosphate level remained fairly constant. This finding might be the result of a decrease of the absorption of phosphate from the alimentary tract.

Citrate metabolism.—On admission, the serum citrate level was low. During cortisone treatment there was a successive increase of the concentration, which, however, remained low as compared to the values found by Harrison & Harrison during vitamin D treatment of rachitic children. The urinary citrate excretion seemed to vary with no relation to the treatment.

Acid-base balance.—Before cortisone treatment the urinary excretion of bicarbonate was relatively high, reaching 9.2 mEq per liter, despite a slight acidosis. However, the ability of the kidneys to conserve fixed base remained intact, since ammonium chloride administered as an acid load caused a fall of the pH of the urine to 5.5 at the same time as the bicarbonate excretion in the urine was reduced to a minimum. After treatment, the carbon dioxide combining power of serum became normalized.

Discussion

The rapid improvement of a patient with typical symptoms of vitamin D intoxication after treatment with cortisone demonstrates the beneficial effect of this therapy. There was a prompt fall of the serum calcium level and a decrease of the calcium excretion in the urine. When the results in our case are compared with those obtained by Anderson *et al.* in cortisone treatment of sarcoidosis complicated by hypercalcemia, it is obvious that the effect on the calcium excretion in the urine was more rapid in our patient with vitamin D intoxication.

There are many indications that cortisone affects calcium metabolism. Pincus, Natelson & Lugovoy have shown that cortisone administration to rabbits causes a rapid fall in the serum calcium concentration at the same time as the citrate level decreases. The effect on the serum calcium level might be due to a reduced absorption of calcium from the intestines. From their balance studies, Anderson *et al.* concluded that there was an increase of the fecal output of calcium after cortisone treatment. Furthermore Soffer, Gabrilove & Jailer have found that cortisone in a patient with Cushing's syndrome induced a very high fecal excretion of calcium causing a negative balance.

Anderson *et al.* have suggested the possibility of a substrate competition mechanism between vitamin D and cortisone. However, this does not seem

very probable since Follis, from pathological anatomical studies of a 15-month-old baby with Cushing's syndrome, has stated that the skeletal changes in this disease are not of the same type as those observed in rickets or late rickets.

The mechanism by which cortisone interferes with vitamin D and calcium metabolism remains obscure.

Summary

Cortisone treatment in a typical case of vitamin D intoxication caused a rapid improvement of the patient. There was a prompt fall in the serum calcium level at the same time as the calcium excretion in the urine was normalized. The cause of the beneficial effect of cortisone in vitamin D intoxication and other conditions complicated by hypercalcemia has been discussed briefly.

Traitement par la Cortisone de l'Intoxication par la vitamine D.

Un traitement par la Cortisone dans un cas typique d'intoxication par la vitamine D a amené une prompte guérison. Il s'est produit une baisse très rapide du Calcium sérique, et en même temps l'élimination du calcium urinaire se régularisait. La cause de l'effet favorable de la Cortisone dans ce cas d'intoxication par la vitamine D, ou dans d'autres affections compliquées d'hypercalcémie élevée, est brièvement discutée.

Cortison-Behandlung bei Vitamin D-Intoxikation.

Bei einem typischen Fall von Vitamin D-Intoxikation bewirkte Cortison-Behandlung eine schnelle Genesung des Patienten. Der Serumcalciumspiegel fiel prompt ab, als sich zur selben Zeit die Calciumausscheidung im Urin normalisierte. Die Ursache des günstigen Effektes von Cortison bei Vitamin D-Intoxikation und anderen mit Hypercalcaemie vergesellschafteten Zuständen wird kurz diskutiert.

Tratamiento con cortisona de un caso de intoxicación por Vit. D.

En un típico caso de intoxicación por Vit. D, el tratamiento con cortisona produjo rápida mejoría al mismo tiempo que caída de la calcemia y normalización de la excreción urinaria de calcio. Se discute brevemente la causa del efecto benéfico de la cortisona en la intoxicacíon por Vit. D y otras afecciones complicadas por hipercalcemia.

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ANNOUNCEMENTS

The First International Congress of Human Genetics

will be held in Copenhagen, Denmark, August 1–6, 1956. This congress is planned to cover all genetic aspects of normal and pathological characters in man. Any person interested in the subject of human genetics and especially of medical genetics is invited to take part in the congress.

Provisional programme and further informations are sent on request.

The Secretariate of the First International Congress of Human Genetics,
The University Institute for Human Genetics, 14, Tagensvej,
Copenhagen, N., Denmark.

The IVth International Congress of Internal Medicine

will be held in Madrid from September 19th to 23rd, 1956, under the presidency of Professor C. Jiménez Diáz. There will be two main subjects, *The role of the adrenals in the pathogenesis and evolution of internal diseases* and *Bronchial asthma and emphysema*, each of which will be developed by a number of speakers dealing with the various aspects of the theme. Communications on the above or on any other subjects of free choice will be admitted.

Secretariat: Drs. J. C. de Oya and J. Gimena, Calle de Hortaleza 90, Madrid.

BOOK REVIEW

Pediatric Clinics of North America, August, 1955. Symposium on Pediatric Urology.

W. B. Saunders Company. Philadelphia, 1955.

During the last five years pediatric urology has been a subject of increasing interest. M. Campbell and T. T. Higgins *et al.* have published books on this subject. Now, in this volume of Pediatric Clinics M. Campbell and twenty-six other prominent authors have given in 19 chapters a very good introduction to this field of medicine. They deal with most of the problems in pediatric urology. Some chapters are more detailed, others more like a short review. The book is recommended especially for pediatricians but also for urologists.

N.-O. Ericsson.

Acta Pædiatrica **45**: 103—113. March 1956

From the Pediatric Department, University of Oslo
(Chief: Professor LEIF SALOMONSEN)

Blood Gas Determinations on Premature Infants

II. Investigations of Premature Infants with Early Neonatal Dyspnea (The Hyaline Membrane Syndrome)

by WILHELM BLYSTAD

The chief features of the Hyaline Membrane Syndrome are:

1. The occurrence, in the course of the first day of life, of a characteristic clinical picture, with dyspnea, respiratory grunts, and cyanosis.

2. If the infant dies the postmortem examination will reveal pathologic anatomic evidence of pulmonary hyaline membranes, and marked atelectases.

The hyaline membrane syndrome (Clifford) has been given great attention in recent years, but it has not as yet been possible to arrive at a clear understanding of the condition. Etiology and pathogenesis are unknown. The clinical diagnosis and definition are uncertain (Ahvenainen). Some doubt has even been raised as to whether or not the hyaline membranes are of any significance in the development of the condition (Gruenwald, Ranström).

The uncertainty which prevails regarding this condition was evident at the conference, Anoxia of the Newborn Infant, held in London in 1951. Gibberd and Jonxis maintainèd that the formation of membranes and the condition of the lungs can hardly be the cause of death in these cases, and that there must exist another, as yet unknown, factor. In the conclusions from the conference the importance of finding a solution of this problem was pointed out: "This problem might be solved by planned functional tests in certain infants presumably likely to come to autospy, and such activity would be more immediately profitable than the detailed search for aetiological causes or precise chemical constitution of the membranes."

Through gas analyses of cutaneous blood, the author has tried to arrive at a functional evaluation of the respiration in patients with this syndrome. The study includes examination of 12 premature infants who all presented the typical clinical picture, i.e., dyspnea, respiratory grunting, and cyanosis. An earlier publication contains a more thorough description of the laboratory methods, and the results obtained on 9 premature infants without respiratory complications.

Laboratory Methods

Cutaneous blood samples obtained by heel puncture, 0.22 ml in volume, were used in the analyses. Oxygen administration to the infant was unchanged during the sampling.

Determinations of the CO_2 and O_2 tensions were carried out by equilibration of the blood sample with a small gas bubble. A modification of the method described by Riley and co-workers was employed.

Part of the same blood sample was transferred to a small centrifuge tube for subsequent centrifuging, and the plasma CO_2 content was determined by the Roughton-Scholander method. Reading of the blood pH was made from Van Slyke's nomogram (Peters and Van Slyke 1931).

The O_2 analyses give accurate information only where conditions of hypoxemia are concerned, i.e., when the O_2 tensions are low. If the O_2 saturation is high, and the O_2 tension lies above the tension of the bubble, 65.4 mm Hg, the results obtained will be too low. This is related to the fact that the volume of the bubble is relatively large in proportion to that of the blood.

Materials

The clinical data for the 12 premature infants that were examined can be summarized as follows:

1. The complications of pregnancy and delivery are shown in Table 1.

2. The birth weights ranged from 1250–2580 g, averaging 1680 g. The patient whose birth weight was 2580 g, exhibited evidences of immaturity in other respects.

3. The symptoms occurred early, a few hours after delivery. The respiration was distinctly labored, with marked inspiratory retractions and prolonged "grunting" expirations. There was a tendency to cyanosis.

4. The physical examination revealed diminished respiratory sounds, and a disproportion between these weak respiratory sounds and the increased respiratory effort. Râles over the lungs were present in some cases and absent in others.

5. In seven of the patients the symptoms showed a progressive tendency, and the infants died in the course of the first two days of life. In three of these cases relatively brief attacks of apnea, lasting 2–3 minutes, occurred in the course of the disease.

6. Five of the patients survived. In these cases the symptoms were somewhat less marked. None of these patients had attacks of apnea. In three cases the symptoms disappeared at the end of the first or at the beginning of the second day of life. The symptoms of the two other patients lasted a little more than two days. The further course did not present any complications from a respiratory point of view. The general condition on discharge from hospital was satisfactory.

7. All the patients received incubator treatment, and 40–60 per cent oxygen was administered. Gastric aspiration was carried out on arrival at the premature nursery. Secretions in the pharynx were repeatedly drained out. The incubator was placed head down in a slanting position of 15 degrees. Oral food administration was avoided in the acute stage. In six cases stimulation by coffein, cardiazol, or lobelin was tried. Antibiotics were administered in the form of penicillin or streptomycin. Hibernation was tried in one case only.

8. Postmortem examinations were performed on all the patients who died. In all the cases autopsy revealed marked lung atelectases. In six of the seven cases hyaline membranes were also found in the lungs. In three cases a development of pneumonic changes was found, and three cases revealed intracranial hemorrhage. The bleeding was relatively moderate, however, and it seems probable that the marked changes in the lungs represented the most important cause of death.

TABLE 1

Complications of pregnancy and birth in 12 premature infants showing symptoms of early neonatal dyspnea.

	Birth weight, g	Complications of pregnancy	Birth complications	Initiation of respiration
Case 1 D	1,440	—	Breach. Slow fetal heart rate.	—
Case 3 D	1,650	—	Premature rupture of the membranes. Breach.	Some cyanosis.
Case 5 D	2,580	—	Induction.	Some cyanosis.
Case 6	2,060	—	—	Transient cyanosis.
Case 14	1,550	Mild toxemia.	Triplet. Version and extraction.	— ?
Case 15	1,400	Mild toxemia.	Triplet. Version and extraction.	— ?
Case 19	1,250	Toxemia.	Induction.	Apnea, 2 minutes.
Case 24	2,140	Toxemia. Eclampsia.	Cesarean section.	20 minutes lapse before satisfactory respiration.
Case 25 D	1,590	Toxemia.	Premature separation of placenta. Induction.	Mild asphyxia. Some crying after aspiration.
Case 26	1,950	—	—	—
Case 27 D	1,270	Severe toxemia.	Cesarean section.	Depression of respiration.
Case 28 D	1,300	—	—	—

Results

The results for the seven premature infants suffering from early neonatal dyspnea who died are found in Table 2. All the analyses showed a considerable, at times very marked, rise in CO_2 tension. The values obtained ranged from 58.7–157.5 mm Hg, averaging 80.1 mm Hg. A comparison of the CO_2 tensions here with the results obtained for premature infants without respiratory complications (Table 4) reveals a difference in the average values of about 40 mm Hg.

The total CO_2 content in plasma showed no corresponding increase, however. The values here ranged from 32.7–56.4 volumes per cent. The

TABLE 2

Analyses carried out on seven premature infants with early neonatal dyspnea. The patients died, and in six cases autopsy revealed atelectasis and hyaline membranes in the lungs. In one case (Case 27) atelectasis was found, but no hyaline membranes. In cases 3, 5, and 28 brief attacks of apnea occurred in the course of the disease.

	Age hours	O_2 tension mm Hg	CO_2 tension mm Hg	Plasma CO_2 content vols. %	pH
Case 1	17	27.0	62.5	50.9	7.15
	19	31.2	58.7	47.6	7.15
Case 3	7	47.2	70.4	56.4	7.14
	$8\frac{1}{2}$	21.4	71.9	47.3	7.05
Case 5	44	23.9	63.9	34.8	6.95
	46	21.6	66.5	32.7	6.90
Cace 24	27	21.2	66.6	42.5	7.03
	29	20.0	70.5	39.9	6.97
Case 25	28	23.0	76.2	43.9	6.99
Case 27	4	44.3	82.7	43.0	6.95
	$5\frac{1}{2}$	38.4	90.5	45.3	6.91
Case 28	3	45.6	91.7	58.2	7.03
	6	25.9	157.5	51.9	6.69
	7	15.7	92.0	42.5	6.87

average, 45.5 volumes per cent, lay a little below the corresponding value for premature infants without respiratory complications.

The combination of very high values for the CO_2 tension and relatively low values for the CO_2 content resulted in a marked reduction of the blood pH. The values for the latter ranged from 6.69–7.15, averaging 6.98.

The O_2 tensions for these seven patients lay between 15.7–47.2 mm Hg. These values indicate that the hypoxemia in some of the cases was rather marked.

The results for the five surviving patients are shown in Table 3. When the clinical symptoms were fully developed the analyses presented about the same picture in these cases as was seen for the patients who died. However, the displacements were less pronounced. The average values for the surviving patients were: CO_2 tension, 58.1 mm Hg. CO_2 content in plasma, 49.4 volumes per cent; and pH, 7.17. The values for O_2 tension ranged from 33.7–49.8 mm Hg, so in these cases too the results were somewhat lower than those for premature infants without respiratory complications. The results indicate a moderate hypoxemia.

TABLE 3

Analyses on five premature infants with early neonatal dyspnea. All the patients survived. In these cases the dyspnea lasted from one to a little more than two days after birth, after which the symptoms quickly disappeared. The sampling was carried out partly in the acute stage, and partly after the dyspnea had subsided.

Age	Dyspnea	O_2 tension mm Hg	CO_2 tension mm Hg	Plasma CO_2 content vols. %	pH
Case 6 5 hours . . .	+	41.1	60.6	52.8	7.18
$7\frac{1}{2}$ „ . . .	+	47.6	63.3	52.9	7.16
27 „ . . .	−	64.5	40.0	49.4	7.34
29 „ . . .	−	62.0	38.1	48.2	7.36
Case 14 14 „ . . .	+	42.8	59.2	51.9	7.18
17 „ . . .	+	—	56.8	50.1	7.19
38 „ . . .	−	59.4	39.1	48.1	7.34
40 „ . . .	−	62.2	37.4	47.3	7.36
Case 15 15 „ . . .	+	33.7	62.6	50.0	7.14
36 „ . . .	+	36.5	51.3	49.6	7.23
$3\frac{1}{2}$ days . . .	−	69.2	42.6	57.2	7.39
$3\frac{1}{2}$ „ . . .	−	62.8	44.3	55.3	7.36
Case 19 3 hours . . .	+	49.8	58.2	43.9	7.11
5 „ . . .	+	45.6	54.1	47.6	7.18
26 „ . . .	−	56.0	44.2	50.3	7.31
48 „ . . .	−	56.9	38.8	49.5	7.36
Case 26 21 „ . . .	+	36.8	53.0	47.4	7.19
43 „ . . .	+	41.4	61.4	47.7	7.12
3 days . . .	−	44.6	43.8	50.7	7.32

For the surviving patients analyses were also carried out in the course of the first few days following the disappearance of the clinical symptoms. These values were found to lie within the range of those for premature infants without respiratory complications.

Comments

A rise in the CO_2 tension of the blood has been demonstrated in premature infants suffering from early neonatal dyspnea. For the patients in the group who died the rise was quite marked. In all the analyses a reduced blood pH was found.

It is natural to suppose that an increased admixture of venous blood to the cutaneous sample has taken place in these instances. This is caused by

TABLE 4

Analyses carried out in the course of the first four days of life on premature infant who showed no symptoms of respiratory disturbances.

	Age days	O_2 tension mm Hg	CO_2 tension mm Hg	Plasma CO_2 content vols. %	pH
Case 2	4	63.8	36.6	42.7	7.32
Case 4	1	64.9	45.8	50.2	7.29
	2	62.7	37.5	50.4	7.38
	3	56.1	33.2	50.2	7.44
Case 9	1	54.1	37.0	53.2	7.41
	2	63.3	35.2	44.1	7.35
	4	61.5	44.4	51.5	7.33
Case 10	1	51.4	45.6	51.9	7.30
	1	53.8	44.8	52.5	7.32
	2	59.0	36.8	43.4	7.32
	4	73.9	28.9	40.2	7.38
Case 12	2	76.4	36.6	44.8	7.34
	3	73.7	41.0	52.0	7.35
Case 13	1	50.1	34.4	44.1	7.36
	4	59.2	36.4	52.5	7.42
Case 17	1	68.1	32.5	43.3	7.37
	4	78.0	39.5	53.6	7.39
Case 20	2	54.5	42.7	53.3	7.35
Case 21	4	71.1	42.2	51.8	7.34
	Average		38.5	48.7	7.35

a right–left shunt through the foramen ovale and ductus Bottali (Lind and Wegelius). A right–left shunt does not, however, usually result in an increase of the CO_2 tension. Furthermore, the alteration of the blood pH caused by this mechanism should be relatively slight on account of the simultaneously occurring reduction of oxyhemoglobin.

The author is therefore of the opinion that there is reason to conclude that the recorded rise in the CO_2 tension is due principally to a respiratory failure. A clinical evaluation reveals increased respiratory efforts in these patients. Investigations carried out by Karlberg and co-workers have further shown that this condition involves an increased minute volume. The respiratory failure could, consequently, hardly be due to a depression of the respiratory center, but must originate from a pulmonary pathological condition.

The marked pathological anatomic findings in the lungs, revealed by the autospsy, confirm this conclusion.

As has been mentioned earlier, some doubt has been raised as to the significance of the pulmonary pathological findings in these cases. The results of these investigations show, however, that a marked respiratory failure of pulmonary origin is the central feature of this condition.

In three of the patients in this material attacks of apnea occurred in the course of the disease. The explanation of these attacks would probably be a transient central respiratory failure. The attacks were relatively brief, lasting from 2–3 minutes, and the dyspnea continued after the attacks. In one of the cases sampling was carried out about 3 minutes after an attack. A considerable rise in the CO_2 tension to 157 mm Hg was found. This finding clearly illustrates the serious implications of attacks of apnea when they occur in patients with neonatal dyspnea.

The CO_2 content in plasma is generally regarded as an indicator of the alkali reserve. The average CO_2 content for the seven patients who died was 45.5 volumes per cent. In these patients, where the CO_2 tension was very high and the blood pH very low, the picture presented will, however, not be adequate. A reduced CO_2 tension, and a consequently more normal pH, would have resulted in a considerably lower level for the CO_2 content in these patients. Peters and Van Slyke (1931) point out that a change in the blood pH of 0.1 will give a change in the CO_2 content of "true plasma" corresponding to 7 volumes per cent. A correction of the pH to 7.35 will thus cause a reduction of the CO_2 content to about 20 volumes per cent for the group of patients who died, and about 37 volumes per cent for the surviving group. A considerable reduction of the alkali reserve was therefore present, particularly in the patients who died. The causes for this metabolic acidosis would probably have to be sought in an increased production and accumulation of organic acids, and in a damaged kidney function.

The most important finding is probably the considerable reduction of the blood pH. Two different factors are of significance in the establishment of the low pH: (1) The respiratory failure, causing a rise in the CO_2 tension, and (2) the reduction of the alkali reserve, probably occurring secondarily. It is probable that the increasing acidemia and complications in the form of attacks of apnea will represent the most important factors causing poor prognosis.

The rather marked hypoxemia is probably to a great extent caused by a right–left shunt (Lind). Consequently, the O_2 analyses do not form a very good basis for an evaluation of the functional condition of the lungs. The hypoxemia probably represents the most important factor in the establishment of the recorded alkali deficiency. It must further be pointed out that

the effect which could be expected from oxygen therapy will depend on the degree of the existing shunt.

In one of the patients in this group the autospy revealed lung atelectasis while hyaline membranes were not found. This patient presented the same clinical picture as the others, and the analyses showed similar displacements in the acid-base balance. Cases with early neonatal dyspnea and no hyaline membranes at autopsy are, in the author's opinion, not very unusual. The significance of the hyaline membranes for this syndrome will still have to be regarded as uncertain. It is possible that the membranes, when they are present, play an important part in the development of the atelectasis; but they could also be secondary findings, and of no great account. With regard to the development of the severe respiratory failure, the author is inclined to lay particular stress on the massive atelectases.

It must be pointed out that in some cases autopsy reveals atelectases and hyaline membranes even if the patients do not present the typical clinical picture with dyspnea. Analayses were carried out in one of these cases. A considerable respiratory acidosis was found, the CO_2 tension being 90.6 mm Hg, and the pH 6.74. From the very beginning this patient showed symptoms of a depression of the respiration. There seems to be reason to believe that the development of the typical clinical picture with dyspnea is dependent on an undamaged respiratory centre.

In the five surviving patients the analyses showed a normalizing of the values. The results confirm the impression that within a short time a radical improvement of the function of the lungs sets in. In the author's opinion the time of this turn of events will be somewhat variable. Potter maintains that the improvement generally occurs within the first few hours. This does not quite conform with the author's observations, nor with those of several other investigators (Clifford, Parmelee). In many cases the symptoms can last 2–3 days before the disease takes a favorable turn.

Oxygen administration is still the most important form of therapy for these patients. It is possible that an increased supply of oxygen to the tissues can reduce the production of organic acids, and improve the kidney function. Through this an increased amount of alkali should be set free to compensate the respiratory acidosis, and the chances of a possibly fatal acidemia should be lessened. It is further possible that the attacks of apnea which tend to aggravate the condition to a considerable extent, could be prevented by energetic O_2 therapy. The effectiveness of the oxygen therapy will, however, depend on the degree of the right–left shunt.

CO_2 administration in cases of atelectasis has been proposed by Nisell. The administration of CO_2 at short, frequent intervals, has been reported by Lichtfield and co-workers. However, on the basis of the results obtained

in the present study the author is inclined to consider the administration of CO_2 as contraindicated for patients suffering from early neonatal dyspnea.

Attempts to correct the metabolic acidosis and the acidemia by administration of alkali would probably not give favorable results. In all likelihood a considerable aggravation of the respiratory acidosis would ensue. Many other therapeutic measures have been proposed and tried, but the results have not as yet been too convincing.

Summary

In premature infants determinations of the CO_2 tension, O_2 tension, plasma CO_2 content and pH of cutaneous blood samples were carried out. In the present publication are reported the results obtained on 12 premature infants suffering from early neonatal dyspnea (the hyaline membrane syndrome). Seven of these patients died, and in 6 of the cases the autopsy revealed hyaline membranes in the lungs.

In the 7 fatal cases there was demonstrated an increased CO_2 tension, an accentuation of the metabolic acidosis, markedly reduced values for the pH and low O_2 tensions indicating a considerable hypoxemia. The investigations confirmed the idea that the pulmonary pathology and the subsequent respiratory failure represent the central features in this condition. The pronounced displacements in the acid-base balance are probably of great significance for the poor prognosis.

The 5 surviving premature infants presenting the same picture showed similar, though less pronounced, displacements in the acid-base balance. The clinical recovery was accompanied by a rapid regression of the recorded disturbances.

Détermination des gaz dans le sang de nourrissons prématurés. II. Recherches chez des nourrissons prématurés présentant une dyspnée néonatale précoce. (Le syndrome de membranes hyalines.)

Des dosages de la tension de CO_2, de la tension d'oxygène, du contenu de CO_2 dans le plasma et du pH du sang cutané ont été fait chez des nourrissons prématurés. Dans la publication présente, l'auteur rapporte les résultats obtenus chez douze nourrissons prématurés souffrant de dyspnée néonatale précoce (le syndrome de membranes hyalines). Sept de ces patients sont morts et chez six de ces cas on a trouvé à l'autopsie des membranes hyalines dans les poumons. On a pu mettre en évidence dans les sept cas fatals une augmentation de la tension de CO_2, une accentuation de l'acidose métabolique, un abaissement prononcé du pH et des tensions d'oxygène basses, indiquant une hypoxémie considérable. Les recherches ont confirmé le fait que les lésions pulmonaires et l'insuffisance respiratoire, qui en résulte, sont les principales caractéristiques de cet état. Le déséquilibre accentué de la balance acido-basique explique probablement bien le pronostic sévère. Chez les cinq nourrissons prématurés qui ont survécu et ont présenté le même tableau clinique, des déséquilibres semblables, quoique moins accentués, dans la balance acido-basique ont pu être démontré. La guérison clinique était accompagnée d'une régression des anomalies enregistrées.

Blutgasbestimmungen bei Frühgeburten. II. Untersuchungen an Frühgeburten mit frühzeitiger Neugeborenendyspnoe. (Syndrom der hyalinen Membranen.)

Bei Frühgeburten wurden Bestimmungen der CO_2-Spannung, der O_2-Spannung, des Plasma CO_2-Gehaltes und des pH von Kapillarblut durchgeführt. In der vorliegenden

Veröffentlichung werden die Ergebnisse, die bei 12 an früher Neugeborenendyspno (Syndrom der hyalinen Membranen) leidenden Frühgeburten gewonnen wurden dargelegt. Sieben dieser Patienten starben und in 6 der Fälle zeigte die Autopsie hyalin Membranen der Lunge. Bei den 7 Fällen mit letalem Ausgang wurden eine erhöht CO_2-Spannung, eine Betonung der metabolischen Acidose, merklich erniedrigte Wert des pH und niedrige O_2-Spannungen, die eine beträchtliche Hypoxaemie anzeigen festgestellt. Die Untersuchungen bestätigten, dass der Lungenschaden und das darau folgende Versagen der Atmung das zentrale Merkmal in diesem Zustand darstellen Die ausgeprägten Entgleisungen im Säure-Basen-Gleichgewicht sind wahrscheinlich von grosser Bedeutung für die ernste Prognose. Die 5 überlebenden Frühgeburten die dasselbe Bild boten, zeigten ähnliche, wenn auch weniger ausgeprägte Verschie bungen im Säure-Basen-Gleichgewicht. Die klinische Genesung war von einer schneller Rückbildung der beschriebenen Störungen begleitet.

Determinación de gases sanguíneos en prematuros. II. Investigacion de prematuros con disnea neonatal.

Se determinó en prematuros, la tensión de O_2 y CO_2, el contenido plasmático de CO_2 y el pH de la sangre periférica. En esta publicación se comunican los resultados obtenidos en 12 niños con disnea neonatal temprana (sindrome de la membrana hialina). Siete de estos pacientes murieron revelando la autopsia la presencia de membrana hialina en 6 de ellos. En todos estos casos se demostró un aumento de la tensión de CO_2, aumento de la acidosis metabólica, reducción de pH y bajos valores de tensión de O_2 indicando considerable hipoxemia. Esta investigación confirma que la patología pulmonar y la subsecuente falla respiratoria representan el hecho principal de esta afección. Los marcados cambios del equilibrio ácido basico son probablemente de gran significación en el mal pronóstico. Los 5 sobrevivientes presentaron el mismo cuadro aunque con menos variaciones en el equilibrio ácido base. La recuperación clínica se acompañaba por una rápida regresión de los cambios.

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Histological Findings Characteristic of Rickets in Foetuses and Young Infants

by

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Only a few observations of changes typical of rickets in the earliest stages of human life have hitherto been published. Until recently the statement made by Schmorl at the beginning of this century has remained unchallenged, namely that rickets does not occur before the middle of the second month of life. Exceptions were made for children of mothers suffering from osteomalacia after Maxwell had been able to prove the existence of very pronounced histological changes in the skeleton of such children dying when only a few days old. During the last decades some investigators have established that roentgenological (7, 14) and biochemical (14) changes characteristic of rickets may occur, especially in premature infants, even during the first month of life, but in these series no histological control of the nature of the changes was available. Recently, however, some investigations have been published showing that skeletal changes characteristic of rickets may occur even in very young infants of mothers who cannot be suspected of having suffered from osteomalacia. Follis, Park & Jackson have investigated a large series of infants less than two years old coming to autopsy; among 360 infants dying during the first two weeks of life "slight rickets" was found in only two, but during the next two weeks rickets was found in 16.2 per cent, 15 per cent being "severe rickets". Ranström & v. Sydow found "definite rachitic changes" in 52.3 per cent of 155 infants dying during their first two weeks; among the 69 infants dying on the first day of life "definite rachitic changes" were found in 29 per cent.

The purpose of the present paper has been:

(1) To investigate the occurrence in the ribs of histological changes characteristic of rickets during foetal life and during the earliest part of postnatal life;

Fig. 1 (top left). Foetus 17 cm, weight 130 g, born 5th month, legal abortion. *Osteochondral junction: normal structure.*

Fig. 2 (top right). Foetus 20 cm, weight 165 g, born 5th month, legal abortion. *Hyperplasia of cartilage at straight osteochondral junction.*

Fig. 3 (right). Foetus 23 cm, weight 300 g, born 5th month, legal abortion. *Hyperplasia of cartilage, irregular osteo-chondral junction with slight mixture of cartilage and bone.*

(2) To record the different characteristics of the changes observed and t investigate their mutual association;

(3) To investigate a possible relation between the presence of such change in the ribs and the presence of certain serum values for calcium, phosphoru and phosphatase in the mother; of roentgenological signs of rickets in th wrist; and of rachitogenic factors in the history;

(4) On this basis, to try to gain a conception of the causes of the histologica changes observed.

Material and Methods

The material for this investigation is derived from three parts of Sweden: (1) Malm (56°N; the Obstetric-Gynaecological Clinic); (2) Uppsala (60°N; the Pathological De partment); (3) Sundsvall (62°N; the Obstetric-Gynaecological and Paediatric Depart ments). In all autopsies on infants and foetuses carried out in these institutions during a two-year period (Uppsala three years) the osteochondral junction, including some centimeters of bone and cartilage at either side of the first or second and the sixth or seventh rib, have been collected. Only a small number of preparations have been lost. Two cases of syphilis congenita and one case of a skeletal malformation resembling chondrodystrophia foetalis have been excluded. The examined series thus consists of *527 individuals*. Its distribution according to place of origin, sex, birth weight, age, and cause of death is shown in Tables 1 and 2.

The birth-weight groups have been delimited so that the first group (0–300 g) should include, above all, most legal abortions. The upper limit corresponds rather well to the border between the fifth and sixth foetal month. The second group (310–1000 g) includes, generally speaking, the remaining abortions and the "nonviable" premature infants. The third group (1010–2500 g) premature infants with "viable" birth-weight, and the fourth group (> 2500 g) infants usually judged as full term. It is obvious from Table 1, that the material from the various towns is very differently distributed among the birth-weight groups, which is, of course, explained by the origin of these three series from different types of institutions.

For each case examined a record has been established, reporting, *inter alia*, the mother's age, obstetric history, health during this last pregnancy, its duration, course, and details of delivery; the infant's state at birth and afterwards, possible causes of

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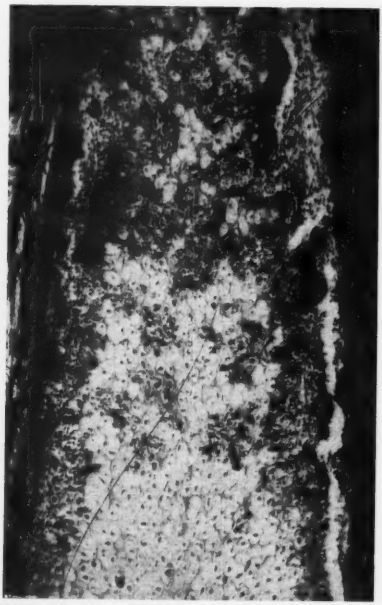
Fig. 4 (top left). Foetus 23 cm, weight 200 g, born 4th month, legal abortion. *Osteo-chondral junction straight with hyperplasia/hypertrophy of cartilage cells.*

Fig. 5 (top right). Foetus 21 cm, weight 200 g, born 5th month, legal abortion. *Intimate mixture of cartilage and bone, cartilage cells hypertrophic.*

Fig. 6 (left). Premature infant, birth weight 1000 g, height 35 cm, born 7th month, died 7 hours after birth. *Osteo-chondral junction straight, hyperplasia of cartilage just visible.*

Fig. 7 (right). Premature infant, birth weight 1000 g, height 37 cm, born 7th month, died hours after birth. *Slightly irregular osteo-chondral junction, cartilaginous hyperplasia/hypertrophy.*



premature birth and death, as well as the mother's marital status and the employment of the parents. In most cases it has also been possible to question the mother about her housing standard and the number of those living with her, her work during pregnancy, time spent outdoors, her consumption of vitamin D and milk as well as other aspects of her diet during pregnancy. In about half the cases it was also possible to obtain a blood sample from the mother, usually during the first day after delivery, for the determination of serum calcium (according to Kramer & Tisdall), of serum inorganic phosphorus (according to Youngburg & Youngburg), and of serum phosphatase (according to King & Armstrong modified by Buch & Buch). Finally, it was usually possible to get a roentgen picture of the left wrist of the infant or foetus before autopsy.

The ribs were fixed in 10 per cent formalin and then partially decalcified in Müller's solution in which the preparations were left until they were just ready for sectioning. After washing in running water for 24 hours, the preparations were embedded in celloidin; frozen sections were prepared and stained with haematoxylin-eosin. This method of preparation is especially suitable for differentiating normally calcified bone from non-calcified osteoid.

At the examination of the histological sections the following characteristics have been recorded: A, the gross histological structure of the osteo-chondral junction; B, the structure of the cartilage at the border of the ossification zone; and C, the occurrence of osteoid.

A. *The gross histological structure of the osteo-chondral junction.* The normal osteo-chondral junction is straight, narrow and distinct. Those cases where this junction is broadened and manifestly irregular have been labelled positive. In this connection the positive findings have been defined, on the one hand, by a stricter definition (A), including only the severe changes with a mixture of cartilage and bone at the osteo-chondral junction, and, on the other hand, by a looser definition (a), including also cases with slighter changes—with an irregular osteo-chondral junction but without mixture of bone and cartilage.

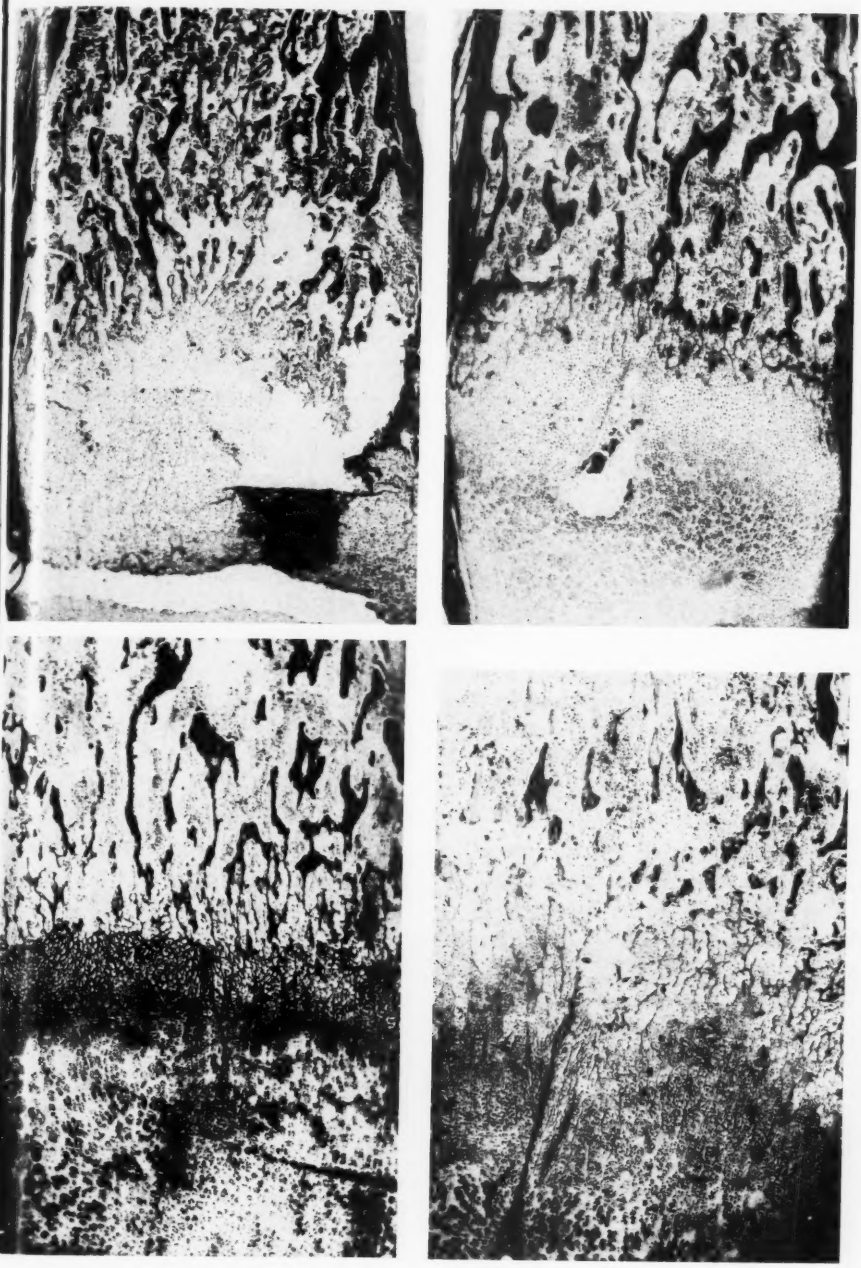
B. *The structure of the cartilage at the border of the ossification zone.* At the cartilage side of the normal ossification zone the cartilage cells are regularly arranged in columns, with the cells often increasing in size towards the ossification zone together with a preparatory calcification of the cartilaginous substance. Those cases where the cartilage cells do not present this regular arrangement but are forming a more or less diffuse carpet of cells of varying size and with irregularly shaped nuclei, have been labelled (B).

Fig. 8 (top left). Premature infant, birth weight 1100 g, died when 10 days old. *Irregular ossification zone with atypical cartilage.*

Fig. 9 (top right). Premature infant, birth weight 1070 g, died when 12 days old. Polycystic kidneys. *Slightly irregular osteo-chondral junction with atypical cartilage.*

Fig. 10 (left). Premature infant, birth weight 1780 g, died when 10 days old. *Slightly irregular ossification zone with moderate atypia of cartilage.*

Fig. 11 (right). Premature infant, birth weight 1800 g, died when 4 days old. Pulmonary haemorrhage. *Advanced irregularity of ossification zone with atypia of cartilage and mixture of cartilage and bone.*



C. *Occurrence of osteoid* is usually considered pathognomonic for rickets. In this series, with the technique applied, small amounts of non-calcified osteoid have been found in the ossification zone in almost every case. Yet, the findings have only been labelled as positive when osteoid has been found in fairly large quantities. In this case, too, one narrower definition (C) has been applied, including only those cases where osteoid was occurring freely even at most central bone lamellae in the spongiosa, and one wider definition (c), including also those cases where the occurrence of osteoid was limited to the ossification zone and the subperiosteal tissue.

Histological Findings

The occurrence of signs and combinations of signs characteristic of rickets is shown in Tables 3, 4 and 5. It will be seen that such signs are common in all age and weight groups and in both sexes, and that the number of cases free of any rachitic signs is in the minority within practically all the groups. The occurrence of such negative cases, however, rises significantly with increasing weight but falls again, though not significantly, in the higher weight groups in live born when compared with stillborn infants.

The low frequency of entirely negative cases is mainly caused by the fact that *osteoid* has been found so commonly. The occurrence of osteoid is highest in the lowest birth-weight groups, then falls steeply and considerably in the stillborn with rising birth weight, so that among the full-term stillborn it is found in only a minority. In the live born dying during the first week of life the occurrence of osteoid is again significantly higher than in the stillborn. This is true for the occurrence of osteoid if defined by the narrower (C) as well as by the wider limitation (c).

Irregular structure of the cartilage with hyperplasia-hypertrophy of the cartilage cells and gross histological *broadening and irregularity of the osteo-chondral junction* are also found in all groups, though less often than the osteoid. The only exception are those cases with the latter sign showing a real mixture of cartilage and bone in the osteo-chondral junction (A) which have not been found among the stillborn full-term infants. In this group the incidence of irregular structure of the cartilage (B) is also significantly lower than in the lower birth-weight groups.

Table 6 demonstrates a definite correlation among the different rachitic signs in the material. The number of cases with a combination of two signs is significantly higher throughout than would be expected in a random distribution.[1]

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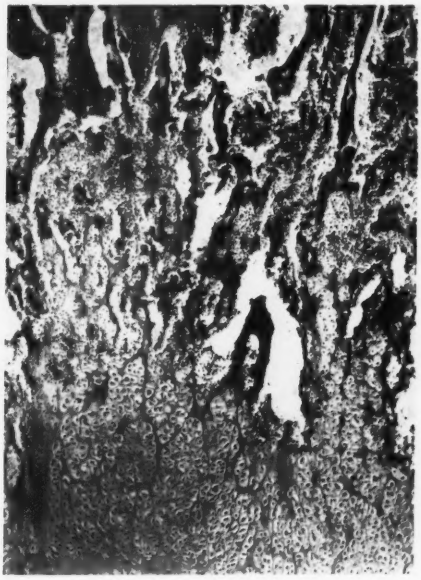
[1] For advice on the method of calculating the correlation we are indebted to Professor Carl-Erik Quensel, Ph.D., Lund.



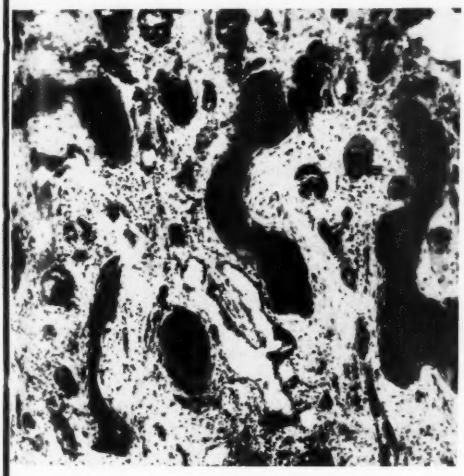


Fig. 12 (top left). Full-term infant, birth weight 3850 g, died when 2 days old. Aspiration during delivery, pulmonary atelectasis. *Regular structure of osteo-chondral junction.*

Fig. 13 (top right). Full-term infant, birth weight 4630 g, died when 2 days old from capillary bronchitis. *Broadening of the ossification zone with atypia of cartilage and mixture of bone and cartilage.*

Fig. 14 (left). *Non-calcified osteoid borders of bone trabeculae.*

TABLE 1

Distribution of the material according to home district, sex, birth weight and age.

d. = day(s); m. = month(s).

Birth weight in g	0–300	310–1000				1010–2500				>2510				*Total Still-born –6 d.*	1010–2500			>2510				*Total All ages*
		Still-born	0 d.	1–6 d.	*Still-born –6 d*	Still-born	0 d.	1–6 d.	*Still-born –6 d.*	Still-born	0 d.	1–6 d.	*Still-born –6 d.*		7–30 d.	1–11 m.	*7 d.–11 m.*	7–30 d.	1–11 m.	*7 d.–11 m.*	*1 year –*	
Malmö . .	*70*	39	12	3	*54*	15	18	9	*42*	34	4	2	*40*	*206*	—	—	—	—	—	—	—	*206*
Uppsala .	—	6	8	3	*17*	22	18	9	*49*	54	14	15	*83*	*149*	8	3	*11*	5	8	*13*	*3*	*176*
Sundsvall	*17*	15	4	1	*20*	25	14	3	*42*	19	11	5	*35*	*114*	3	1	*4*	5	17	*22*	*5*	*145*
Boys . . .	*47*	32	11	2	*45*	33	31	12	*76*	53	15	13	*81*	*249*	3	4	*7*	7	15	*22*	*3*	*281*
Girls . . .	*28*	24	13	5	*42*	29	19	9	*57*	54	14	9	*77*	*204*	8	—	*8*	3	10	*13*	*5*	*230*
Sex undetermined	*12*	4	—	—	*4*	—	—	—	—	—	—	—	—	*16*	—	—	—	—	—	—	—	*16*
Total . .	*87*	60	24	7	*91*	62	50	21	*133*	107	29	22	*158*	*469*	11	4	*15*	10	25	*35*	*8*	*527*

TABLE 2

Cause of death.

Birth weight in g	0–300	310–1000				1010–2500				>2510				*Total Still-born –6 d.*	1010–2500		>2500			*Total All ages*
		Still-born	0 d.	1–6 d.	*Still-born –6 d.*	Still-born	0 d.	1–6 d.	*Still-born –6 d.*	Still-born	0 d.	1–6 d.	*Still-born –6 d.*		7–30 d.	1–11 m.	7–30 d.	1–11 m.	1 year –	
Legal abortion:																				
Medico-social, eugenic, psychiatric indications	*66*	19	—	—	*19*	—	—	—	—	—	—	—	—	*85*	—	—	—	—	—	*85*
Medical indications	*3*	4	—	—	*4*	1	—	—	*1*	—	—	—	—	*8*	—	—	—	—	—	*8*
Other abortions	*18*	30	—	—	*30*	—	—	—	—	—	—	—	—	*48*	—	—	—	—	—	*48*
Macerated foetus	—	1	—	—	*1*	16	—	—	*16*	15	—	—	*15*	*32*	—	—	—	—	—	*32*
Maternal illness (death)	—	5	2	2	*9*	19	10	2	*31*	12	2	1	*15*	*55*	—	—	1	1	—	*57*
Malformations .	—	—	1	—	*1*	4	8	1	*13*	1	8	3	*12*	*26*	2	—	2	7	1	*38*
Birth injury . .	—	—	—	—	—	2	7	5	*14*	26	12	2	*40*	*54*	1	—	—	—	—	*55*
Asphyxia, atelectasis, respiratory infection .	—	1	—	—	*1*	6	5	2	*13*	29	2	9	*40*	*54*	3	2	—	2	—	*61*
Prematurity . .	—	—	21	5	*26*	—	20	9	*29*	—	2	—	*2*	*57*	5	1	—	—	—	*63*
Other known causes	—	—	—	—	—	—	—	2	*2*	—	—	4	*4*	*6*	—	1	4	14	7	*32*
Cause unknown	—	—	—	—	—	14	—	—	*14*	24	3	3	*30*	*44*	—	—	3	1	—	*48*
Total	*87*	60	24	7	*91*	62	50	21	*133*	107	29	22	*158*	*469*	11	4	10	25	8	*527*

TABLE 3

Occurrence of rachitic signs in different groups.

A = Cartilage—shaft junction broadened, irregular, with real mixture of bone and cartilage. a = Cartilage—shaft junction broadened, irregular, all cases. B = Cartilage cells near the ossification zone hyperplastic-hypertrophic forming a diffuse carpet without regular columns. C = Osteoid present even at the central trabeculae of the spongiosa. c = Osteoid present, all cases. – – – = No rachitic signs. In the lower weight groups the figures in the Total columns do not always equal the sums of the figures for boys and girls since in some cases the sex was undetermined.

Birth weight in g	0–300	310–1000		1010–2500		> 2510		*Total Stillborn –6 days*	> 310				*Total All ages*
		Still-born	0–6 days	Still-born	0–6 days	Still-born	0–6 days		Still-born	0–6 days	7 d.–11 m.	> 1 year	
Boys													
ABC	6	1	1	—	2	—	2	*12*	1	5	4	—	*16*
A	6	1	1	—	2	—	2	*12*	1	5	4	—	*16*
a	11	4	2	6	10	3	4	*40*	13	16	9	—	*49*
B	14	4	2	9	7	2	5	*43*	15	14	6	—	*49*
C	24	20	6	7	19	8	6	*90*	35	31	10	1	*101*
c	33	22	10	17	34	22	15	*153*	61	59	18	1	*172*
– – –	12	10	3	14	8	29	13	*89*	53	24	9	2	*100*
Number examined	47	32	13	33	43	53	28	*249*	118	84	29	3	*281*
Girls													
ABC	1	2	1	1	—	—	—	*5*	3	1	1	—	*6*
A	1	2	2	1	—	—	—	*6*	3	2	1	—	*7*
a	5	4	7	9	5	6	3	*39*	19	15	8	—	*47*
B	4	3	5	7	5	3	3	*30*	13	13	5	—	*35*
C	13	16	12	9	14	2	4	*70*	27	30	12	1	*83*
c	21	22	14	16	21	16	11	*121*	54	46	14	2	*137*
– – –	7	2	4	9	7	36	9	*74*	47	20	4	3	*81*
Number examined	28	24	18	29	28	54	23	*204*	107	69	21	5	*230*
Total													
ABC	8	3	2	1	2	—	2	*18*	4	6	5	—	*23*
A	8	3	3	1	2	—	2	*19*	4	7	5	—	*24*
a	19	9	9	15	15	9	7	*83*	33	31	17	—	*100*
B	22	7	7	16	12	5	8	*77*	28	27	11	—	*88*
C	43	39	18	16	33	10	10	*169*	65	61	22	2	*193*
c	63	47	24	33	55	38	26	286	118	105	32	3	*321*
. . . . .	23	12	7	23	15	65	22	*167*	100	44	13	5	*185*
Number examined	87	60	31	62	71	107	51	*469*	229	153	50	8	*527*

TABLE 4

Occurrence of different combinations of rachitic signs in weight and age groups. For explanation, see Table 3.

Birth weight in g	0–300	310–1000		1010–2500		>2510		*Total Stillborn –6 days*	>310				*Total All cases*
		Still-born	0–6 days	Still-born	0–6 days	Still-born	0–6 days		Still-born	0–6 days	7 d.– 11 m.	1 year –	
ABC	8	3	2	1	2	—	2	*18*	4	6	5	—	*23*
aBC	12	3	6	4	6	1	4	*36*	8	16	*8*	—	*44*
ABc	8	3	2	1	2	—	2	*18*	4	6	5	—	*23*
aBc	*13*	*3*	*6*	*6*	*7*	*2*	*5*	*42*	*11*	*18*	*8*	—	*50*
–BC	6	4	1	2	4	—	1	*18*	6	6	2	—	*20*
–Bc	*8*	*4*	*1*	*7*	*5*	—	*2*	*27*	*11*	*8*	*2*	—	*29*
A–C	—	—	1	—	—	—	—	*1*	—	1	—	—	*1*
a–C	4	4	3	2	5	1	—	*19*	7	8	4	—	*23*
A–c	—	—	1	—	—	—	—	*1*	—	1	—	—	*1*
a–c	*6*	*4*	*4*	*5*	*7*	*5*	—	*31*	*14*	*10*	*4*	—	*34*
AB–	—	—	—	—	—	—	—	—	—	—	—	—	—
aB–	—	—	—	*1*	—	*1*	—	*2*	*2*	—	*1*	—	3
––C	21	28	8	8	18	8	5	*96*	44	31	8	2	*106*
––c	*36*	*36*	*13*	*15*	*36*	*31*	*19*	*186*	*82*	*68*	*18*	*3*	*207*
–B–	*1*	—	—	*2*	—	*2*	*1*	*6*	*4*	*1*	—	—	*6*
A––	—	—	—	—	—	—	—	—	—	—	—	—	—
a––	—	*1*	—	*3*	*1*	*1*	*2*	*8*	*5*	*3*	*4*	—	*12*
–––	*23*	*12*	*7*	*23*	*15*	*65*	*22*	*167*	*100*	*44*	*13*	*5*	*185*
Number examined	87	60	31	62	71	107	51	*469*	229	153	50	8	*527*

TABLE 5

Occurrence of different rachitic signs and combinations of rachitic signs in weight and age groups. *Percental distribution.* For explanation, see Table 3.

Birth weight in g	0–300	310–1000		1010–2500		>2510		*Total Stillborn –6 days*	>310				*Total All ages*
		Still-born	0–6 days	Still-born	0–6 days	Still-born	0–6 days		Still-born	0–6 days	7 d.–11 m.	*Stillborn –11 m.*	
A	9.2	5.2	9.7	1.6	2.8	—	3.9	*4.1*	1.7	4.6	10.0	*3.7*	*4.6*
a	21.8	15.0	29.0	24.2	21.1	8.4	13.7	*17.7*	14.4	20.3	34.0	*18.7*	*19.0*
B	25.3	11.7	22.6	25.8	16.9	4.7	15.7	*16.4*	12.2	17.6	22.0	*15.3*	*16.7*
C	49.4	65.0	58.1	25.8	46.5	9.3	19.6	*36.5*	28.4	40.5	44.0	*35.2*	*37.0*
c	72.4	78.3	77.4	53.2	77.5	35.5	50.0	*60.0*	51.5	68.6	64.0	*59.7*	*60.9*
ABC	9.2	5.0	6.5	1.6	2.8	—	3.9	*3.8*	1.7	3.9	10.0	*3.5*	*4.4*
aBc	14.9	5.0	19.4	9.7	9.9	1.9	9.8	*9.0*	4.8	11.8	16.0	*8.6*	*9.5*
–Bc	9.2	6.7	3.2	11.3	7.0	—	3.9	*5.8*	4.8	5.2	4.0	*4.9*	*5.5*
a–c	6.9	6.7	12.9	8.1	9.9	4.7	—	*6.6*	6.1	7.2	8.0	*6.7*	*6.6*
aB–	—	—	—	1.6	—	0.9	—	*0.4*	0.9	—	2.0	*0.7*	*0.5*
– –c	41.4	60.0	41.9	24.2	50.7	29.0	37.3	*39.7*	35.8	44.4	36.0	*38.9*	*39.3*
–B–	1.1	—	—	3.2	—	1.9	2.0	*1.3*	1.7	0.7	—	*1.2*	*1.1*
a– –	—	1.7	—	4.8	1.4	1.0	4.0	*1.7*	2.2	2.0	8.0	*2.8*	*2.3*
– – –	26.4	20.0	22.6	37.1	21.1	60.7	43.1	*35.6*	43.7	28.8	26.0	*36.3*	*35.1*
Number examined	87	60	31	62	71	107	51	*469*	229	153	50	*432*	*527*

TABLE 6

Correlation between different histological signs of rickets. All cases, stillborn up to 6 days of age.

Combination	Total number examined N	Number of cases with 1st sign R	Number of cases with 2nd sign K	Number of cases with both signs n	Expected number of cases with both signs $\tilde{n}$	Diff. $(n-\tilde{n})$	$\mathcal{E}$ Diff. $(n-\tilde{n})$ $\left(\mathcal{E}^2 = \tilde{n}\frac{N-R}{N}\frac{N-K}{N-1}\right)$
AB . .	469	19	77	18	3.1	14.9	±1.58
AC . .		19	169	19	6.9	12.1	±2.06
Ac . .		19	286	19	11.6	7.4	±2.10
BC . .		77	169	54	28.1	25.9	±3.86
Bc . .		77	286	69	47.0	22.0	±3.93
aB . .		83	77	44	13.6	30.4	±3.04
aC . .		83	171	55	30.3	24.7	±3.95
ac . .		83	286	73	50.6	22.4	±4.02

Roentgenological Examination

In 309 cases satisfactory roentgen pictures of the left wrist have been obtained after death. They have been interpreted consecutively by the same examiner who did not know the histological findings or the histories. The results appear in Table 7.

By far the majority of the examined wrists show a "normal" picture, i.e., the epiphyseal line is straight and even without spurs, fringes, cupping or broadening, and the bone ends show the same degree of calcification as the rest of the bones. This applies to all weight and age groups; in the group of full term infants dying during their first week no deviations from normal were observed. Most aberrations were found in the lowest weight group; they were always slight and only in a few cases more than one type of abnormality was found in the same roentgen picture.

That abnormalities were observed not only in cases where histologically rachitic signs had been found but also in cases completely free of histological signs of rickets is seen in the table. This is especially true of the cases in the lowest weight group. Perhaps a certain accumulation of "positive" roentgen findings may be discerned in the few cases presenting a histologically fully developed rachitic structure (ABC) but this accumulation is by no means significant. On the other hand, it is obvious that the "positive" roentgen findings are not only mainly found in the lowest weight group but also that within this group they are mainly observed among the smallest cases: out of 17 "positive" findings among the 35 cases in the weight group 0–300 g, 13 oc-

TABLE 7

Roentgenological findings.

Birth weight in g. Age. Histological findings	Number examined	Cortical spur		Fringing		Cupping Ulna	Metaphyseal decalcification		Normal findings
		Ulna only	Ulna and radius	Ulna only	Ulna and radius		Ulna only	Ulna and radius	
0–300	*35*								
ABC	6	2	1	1	1	—	1	—	2
Other "positive"	20	6	—	—	—	—	—	—	14
– – –	9	3	2	—	—	—	—	—	4
310–1000	*54*								
ABC	4	1	—	—	—	—	—	—	3
Other "positive"	34	—	—	—	—	—	—	1	32*
– – –	16	—	—	—	—	—	—	1	15
1010–2500 (Stillborn–6 days)	*82*								
ABC	2	—	—	—	—	—	—	—	2
Other "positive"	53	—	1	—	—	—	—	2	50
– – –	27	—	—	—	—	—	—	1	26
> 2510 (Stillborn–6 days)	*112*								
ABC	1	—	—	—	—	—	—	—	1
Other "positive"	48	—	—	—	—	—	—	—	48
– – –	63	—	—	—	—	—	—	—	63
> 1010 (> 7 days)	*26*								
ABC	3	—	—	—	—	1	1	—	2
Other "positive"	15	—	—	—	—	1	—	—	14
– – –	8	—	—	—	—	—	—	—	8
Total	*309*	13	4	1	1	2	2	5	284

* In one case the distal end of the ulna on X-ray was found to be shorter than the radius; there was cupping but no broadening and normal calcification: Probably a malformation.

curred among the 17 cases below 200 g. It seems reasonable, therefore, to connect the roentgenological abnormalities observed with the poor development of the skeleton in these cases rather than with rachitic changes.

It should, however, be recalled that the roentgen examinations were made on wrists while the histological examinations were made on ribs and it is conceivable that rachitic changes may have developed differently in different parts of the skeleton. It should perhaps also be mentioned that roentgenological changes will naturally not be seen until some time after the histological changes have started (Rector).

Aetiological and Pathogenetical Factors

From the foregoing it will be clear that in all weight and age groups in his series the following cases have been observed: (1) cases where the osteo-hondral junctions of the ribs should, following generally accepted criteria, be considered normal (– – –); (2) cases where the histological structure completely fulfills the criteria for rickets established by, e.g., Follis, Jackson, Eliot & Park (ABC); and (3) numerous cases where the histological picture, though not completely normal, does not fulfill all the criteria for the diagnosis of rickets. It remains, then, to find out if the rachitic pictures observed can really, aetiologically and pathogenetically, be considered to be rickets.

According to current concepts rickets is caused by an insufficient mineral supply to the skeleton which in turn is usually caused by an insufficient supply of vitamin D; it may also arise from inadequate intake of minerals or by insufficient absorption of minerals from other causes than lack of vitamin D; perhaps also by abnormally increased excretion of minerals. Some investigators also still recognize the possibility that hereditary and constitutional factors play a role in the development of rickets.

We have tried, as far as possible, to investigate the connection between such aetiological and pathogenetical factors and the occurrence of rachitic signs in our series. We had to depend mainly upon answers of the mothers after the abortion or after the death of the infant. It goes without saying that answers obtained under such circumstances will be highly influenced by sentimental and other factors, thus reducing their reliability. It is probable, on the other hand, that these factors will act in the same direction upon the answers from mothers of "rachitic" and of "non-rachitic" offspring, since neither the mother nor the interviewer could know at that time what the result of the histological examination would be. Making allowance for these factors, we have found it of interest to see if they point in a distinct direction.

Vitamin D supply.—In 308 cases the mothers had reported whether or not they had taken some vitamin D preparation during pregnancy. Forty-eight mothers reported having taken vitamin D, all the rest denying vitamin D intake. As was to be expected, it was mainly mothers of infants and foetuses with a birth weight over 1000 g who had taken vitamin D. In many cases the prophylaxis had probably been unsatisfactory, irregularly carried out, or used only for a short time. Among 13 mothers of offspring presenting a fully developed histological picture of rickets (ABC), there is a positive statement of vitamin D prophylaxis in one case, i.e. a foetus of 5 months weighing 200 g, the mother stating she had taken cod liver oil (dose unknown) for one month of the pregnancy.

No positive or negative correlation[1] could be demonstrated between a history of prenatal vitamin D prophylaxis and the occurrence of different histological signs of rickets. This is true also after division of the series into weight and age groups.

Exposure to sunlight.—In 308 cases the mothers had stated if they had taken daily walks, had had outdoor work or a summer holiday during pregnancy. To decide from this the extent to which they may have been exposed to sunlight is certainly very difficult. As criteria for "exposure to sunlight" we took the statement of the mothers that they (1) used to walk for at least two hours daily, (2) used to work outdoors, (3) used to walk for at least an hour and spent a shorter summer holiday during pregnancy, or (4) had spent a longer summer holiday, at least one month, in the country.

No correlation could be proved between exposure to sunlight, thus defined, and the presence or absence of histological signs of rickets in the offspring.

Geographical distribution.—In comparing the occurrence of different histological signs in the series coming from Malmö, the southernmost, and Sundsvall, the northernmost place, it was generally found that they occurred in the frequency to be expected in a random distribution, but that the number of cases free from every sign of rickets (– – –) in the Malmö series was significantly lower than expected. An increased occurrence of histological signs of rickets associated with the long sunless winters of northern Sweden could thus not be demonstrated.

Mineral intake.—In 308 cases the mothers have stated the approximate amount of milk consumed daily during pregnancy and whether they had eaten cheese adequately, moderately or scantily. As "sufficient mineral intake" we have chosen to consider a daily quota of at least half a liter of milk plus moderate or adequate cheese consumption, or at least three quarters of a liter of milk plus scanty or no cheese consumption.

No association could be found between mineral intake, thus defined, and the occurrence or absence of histological signs of rickets in this series.

Serum calcium, serum inorganic phosphorus, and serum phosphatase in maternal blood.—In 249 cases the amount of calcium, inorganic phosphorus and phosphatase could be determined, usually within the first 24 hours after delivery, in some instances later during the first week. No association could be proved between the maternal serum values and the histological structure of the skeleton of the offspring.

Number and sequence of pregnancies and lactations. Numerous pregnancies in close sequence and especially prolonged previous lactations have been supposed to deplete the maternal mineral stores thereby predisposing the

[1] The correlations are, as mentioned before, calculated following the advice of Professor Carl-Eric Quensel, Lund.

foetus for rickets (6). In this series multiparity occurs mainly in those mothers having abortions in the weight group 0–300 g, where it has probably contributed often to the motivation of legal abortion on medico-social indications. No association could be found between a history of three to eight previous pregnancies and the presence or absence of histological signs of rickets in the foetuses.

Social conditions.—Living under inferior social conditions may, no doubt, be combined with an increased risk of suboptimal nutrition of the foetus in utero, among other things concerning minerals and vitamin D. We have therefore investigated the following social factors: the marital state of the mother; her employment, if any; the employment of the husband; the quality of housing and the degree of crowding; the number of children. As "unsatisfactory social conditions" we have chosen to consider those situations where the mother has been unmarried or the husband had no steady employment, where the family had no house of their own or where the dwelling was estimated as very unsatisfactory, and where the degree of crowding was reported as at least three inhabitants per room (except kitchen).

Reports of this kind have been available in 316 cases. No significant correlation could be established between the occurrence of "unsatisfactory social conditions" and the presence or absence of histological signs of rickets.

Summing up the comparisons so far made, it can be said that *nothing has shown that shortage in vitamin D or mineral supply of the pregnant woman may have been of importance for the development of the histological signs of rickets observed in the foetuses and children in this series.*

Sex distribution.—Some investigators (1, 15, 16) have found that clinical rickets occurs about twice as often in boys as in girls. In this series no association could be proved between male sex and the occurrence of different histological signs of rickets. Not even in the lowest weight group (0–300 g) where fully developed histological rickets (ABC) was found in six male foetuses and only in one female is the difference statistically significant.

The rachitic changes observed in this series, then, do not seem to behave like clinical rickets concerning the sex distribution.

Twins.—The series includes nine pairs of twins where preparations have been collected from both twins: six of these being dizygotic and three enzygotic. Beside these, there are thirteen pairs of twins where only one twin has been examined: in three of these the other twin has also died but preparations have not been obtained for different reasons; in ten cases the other twin survived.

In eight of the nine "complete" pairs both twins showed identical histological pictures; they all died on the second day of life or earlier. In the ninth

pair there was no full agreement: the smaller twin, a boy weighing 820 g at birth and dying on the first day of life, showed a "normal" bone (– – –) while the bigger, a boy weighing 1190 g and dying on the second day, presented osteoid (– –C). This pair was dizygotic.

In seven of the ten surviving twins the results of examinations made at Children's Welfare Centres during the first years of life could be gathered. In four of these no signs of rickets had been observed: the findings in the dead twin in these cases were (– – –), (– – –), (– –C), (–BC), respectively. In one case craniotabes (++) and rosary (+) had been observed at the age of 4 months; after increasing the dose of vitamin D craniotabes (+), but no rosary, was still present at 5 months. The finding in the stillborn dizygotic twin was here (a–c). In a sixth pair of twins where the stillborn enzygotic twin presented the structure (aBC) only a slight Harrison's groove was found in the surviving twin at the age of three years; she had not been examined in the meantime and had taken vitamin D every winter.

The greatest interest is linked to a case where the dead dizygotic twin, a boy weighing 1810 g at birth and dying on the second day of life, presented a fully developed histological picture of rickets (ABC). The surviving brother, weighing 1620 g at birth, was first treated at a Children's Hospital for 6 weeks and then in his home where he was supervised by the Children's Welfare Centre. He took, at least from the age of 5½ months, a large dose of vitamin D (3000 I.U.) daily. At repeated examinations between 5½ and 10 months of age he presented epiphyseal bosses and looked pale: the diagnosis of rickets was underlined in the record. On follow-up investigation at the age of three years he showed no skeletal changes except a slight Harrison's groove and the roentgen examination of the wrists, ankles and ribs showed a normal bone structure, except for a certain thickening of the fibular and tibial epiphyses.

It appears, then, from the comparisons between them that twins, enzygotic as well as dizygotic, usually show an identical histological structure of the osteochondral junctions of the ribs. In one case where one twin dying during the newborn period showed fully developed histological rickets, the surviving twin showed clinical signs of rickets later during infancy. From this, of course, no general conclusions can be drawn.

Discussion

It appears from the tables that cases with a fully developed histological picture of rickets (ABC) occur, though sparsely, in all weight groups of our series. On the other hand, cases entirely free of histological signs of rickets (– – –) also occur, much more commonly, in all groups and the incidence

of these negative cases rises significantly with increasing birth weight, so that in the group of full-term stillborn infants they form a majority. The incidence of negative cases, however, again falls, though not significantly, in those surviving birth. A corresponding decrease with rising birth weight and increase with extrauterine life has been proved for the occurrence of osteoid (C) and may perhaps be traced also for the occurrence of the other histological signs of rickets (A, B) as well as for the fully developed histological picture of rickets (ABC).

These observations are obviously in contrast to those made by Follis, Park & Jackson in their series. Among 360 infants dying within the first two weeks of life they only observed two cases of "acute slight rickets", and among 162 stillborn infants no case of rickets. The difference probably cannot depend on different norms of judgement; from the text as well as the illustrations of their paper it seems as if the definition of positive cases in our series was narrower rather than wider as compared with theirs. The difference may be partly explained by the fact that probably no abortions were included in the series of stillborn infants of Follis *et al.*, and that perhaps most cases of their series corresponded to the highest birth-weight group of our series, in which also no cases of fully developed rickets were found among the stillborns. In addition, it cannot, of course, be excluded that the difference in findings may depend on a geographically or anthropologically conditioned difference between the two series.

An elucidation of the mechanism of development of the histological changes observed will meet with considerable difficulties. No doubt it is connected with a dissociation between the growth and the mineralization of the skeleton. Mineralization does not occur at the same rate as growth, and the bone, thereby getting rich in osteoid, becomes less resistant to mechanical action, which may be supposed to promote the development of structural irregularities. The structural irregularities and the atypical cartilage formation, of course, might also be put more directly in connection with a metabolic disturbance of the bone tissue. The tables show that the occurrence of osteoid is followed by these structural irregularities in only a minority of the cases. This could be interpreted that the defective mineralization must reach a certain minimal degree or a certain minimal duration, or both, before the other changes will occur. Considerable amounts of osteoid have been found so often, especially in the earliest foetal stages, that this could nearly be regarded as "physiological". Since the other partial phenomena, and especially the combination of all the partial components of the rachitic picture, however, occur much less frequently, it must be supposed that the defective mineralization will rarely reach the degree of severity that the tenacity of the bone will be risked and structural irregularities manifested during foetal

life. This, therefore, ought to be interpreted as a definitely pathological condition.

The changes observed have presented the same histological characte independently of whether they have been observed during the foetal stag or later. One would, therefore, initially expect them to have essentially th same mechanism of development in both cases. The discrepancy betwee bone growth and mineralization which seems to be the basis of these change may of course have several causes, and these may be supposed to play different role during different developmental stages. It may be caused by defective power of the bone to absorb minerals; by an insufficient minera supply; by shortage of vitamin D; perhaps also by hormonal factors (12) It is known that during the first few weeks of postnatal life the mineral supply to the infant is so scanty that a depletion of minerals must occur (13). Som observations indicate that this may lead to rachitic changes, at least i premature infants (14). On the other hand, it may be considered as established that rickets occurring later during infancy when mineral supply i not usually scanty, will generally presuppose a shortage of vitamin D.

Contrary to this, nothing is known concerning the role of these mineralizing factors in the development of the rachitic changes observed even in foetal life, except in infants of osteomalacic mothers (8). In our series we have not been able to find anything indicating a connection between the mineral intake or the vitamin D supply of the mother and the occurrence of rachitic changes in the foetus. However, the statements on which we had to base our comparisons are so unreliable that such a connection can by no means be excluded. Since it cannot be proved, it will perhaps be necessary to consider also the possibility of some other mechanism of development for the intrauterine changes.

It seems plausible, then, to connect them with the well-known fact that during infancy certain children are liable to develop pronounced rachitic changes in spite of the fact that rachitogenic factors have been present only to a slight degree and for a short time, while in other children no rachitic signs whatever can be proved despite the fact that they have been living for a long time in markedly rachitogenic circumstances. It must be presumed that a certain "liability" for rickets is necessary for the different rachitogenic factors to provoke the clinical symptoms.

Obviously, the existence of such an individually different liability to develop rickets is also imaginable for foetal life. This would explain the fact that no association can be proved between the occurrence of histological signs of rickets and the nutritional status and living conditions of the pregnant women in this series. As to the causes of this varying liability, this question must for the present be left unanswered. It may be connected with different

rates of growth during different periods; with the available stores and the supply of minerals and of vitamin D during different stages of development; with the functional status of endocrine organs, perhaps especially of the parathyroid; with hereditary factors. The higher prevalence of clinical rickets in boys than in girls certainly points towards one of the two last-mentioned suggestions. Even other causes may be imagined; but our ability to penetrate deeper into this problem seems very small at present.

A question of great interest is, of course, whether the "liability" for rickets in infants may have some connection with the foetal bone changes observed by us. Could it be that in some cases the discrepancy between bone growth and mineralization observed in the majority of small foetuses will not be healed by mineralization during the last foetal months but still persist together with the structural irregularities after birth? Further, could it be that in these cases of persisting foetal rickets clinical symptoms of rickets will especially easily develop as a result of inadequate mineral supply during the newborn period and of inadequate supply of vitamin D during infancy—while in those cases where the foetal signs of rickets had never existed or had healed before birth no such liability will be found for rachitic symptoms in the presence of rachitogenic factors? These questions, however, cannot be answered on the basis of present knowledge.

Summary

The osteo-chondral junctions of the first or second and the sixth or seventh rib have been removed from foetuses and infants in 527 consecutive autopsies and examined histologically for the occurrence of changes typical of rickets. The distribution of the series following birth weight and age appears from Table 1. The following histological changes have been searched for: A, Broadening and gross irregularity of the osteochondral junction; B, irregular arrangement of the cartilage cells at the ossification zone; C, occurrence of considerable amounts of osteoid at the ossification zone and in the spongiosa. Concerning two of the changes one narrower (A, C) and one wider (a, c) definition have here been used.

All these histological changes have been found in all weight and age groups (Table 3). A marked correlation has been proved between the different changes (Table 6). The fully developed histological picture of rickets (ABC) likewise has been found, though sparsely, in all weight and age groups of the series, except in the stillborn infants of the highest weight group (the full term). On the other hand, an entirely "normal" bone structure, free from histological signs of rickets, has also been found in all weight and age groups. The incidence of cases with such "normal" findings is significantly higher in the higher weight groups than in the lower ones, and higher, though not significantly so, in the stillborn than in those who lived after birth.

In 309 cases roentgen pictures of the left hand have been made prior to autopsy. These pictures have been normal in most cases. Slight roentgenological changes have been observed mainly in foetuses of less than 300 g of weight, and they have been found in those showing histological signs of rickets as well as in the others.

We have searched for a possible association between the histological findings and the following factors: Vitamin D intake and exposure to sunshine of the mothers during pregnancy, home district of the mothers (Malmö 56°N, Uppsala 60°N, or Sundsvall 62°N), their mineral supply during pregnancy, the levels of calcium, inorganic phosphorus and phosphatase in their blood serum following delivery, their number of children, the sequence of pregnancies and lactations, and social conditions. Nothing has appeared indicating that shortage of vitamin D or defective supply of minerals to the pregnant mother are of importance for the development of the histological findings in the foetus or child.

The interpretation of the findings is difficult. Apparently the changes in bone structure are caused by a discrepancy between bone growth and mineralization, but the cause of this discrepancy is open to discussion.

Aspects histologiques caractéristiques du rachitisme chez des foetus et des nourrissons

Au cours de 527 autopsies de fœtus ou de nourrissons on a procédé systématiquement à l'ablation de la jonction ostéo-chondrale de la première ou deuxième côte, et de la 6e ou 7e côte, puis à leur étude histologique. Les modifications histologiques suivantes ont été constatées : élargissement et aspect irrégulier de la jonction ostéo-chondrale, disposition irrégulière des cellules du cartilage au niveau de la zone d'ossification, apparition d'une quantité considérable de tissu ostéoïde dans la zone d'ossification et la couche spongieuse. Ces modifications histologiques ont été observées, avec une remarquable association, dans tous les groupes quels que soient l'âge ou le poids. L'aspect histologique du rachitisme typique a été également retrouvé, quoique plus rarement, dans tous les groupes de poids et d'âge, sauf dans le groupe des morts-nés de poids élevé. Le nombre de cas présentant une image normale était nettement supérieur dans le groupe d'enfants de poids élevé, que dans le groupe d'enfants de poids plus bas. Dans 309 cas, un examen radiologique de la main gauche avait été réalisé avant l'autopsie. De discrètes modifications radiologiques ont été notées, surtout chez des fœtus moins de 300 g, mais elles furent observées aussi bien chez ceux présentant un aspect histologique de rachitisme que chez les autres. On n'a pu établir aucun rapport entre une insuffisance de vitamine D ou un manque de minéraux chez la mère, et l'évolution de ces modifications histologiques chez le fœtus ou l'enfant. En apparence, ces anomalies de structure osseuse sont provoquées par une discordance entre la croissance osseuse et la minéralisation. La cause de cette discordance reste cependant à discuter.

Für Rachitis charakteristische histologische Befunde bei Foeten und jungen Säuglingen.

Die osteo-chondrale Verbindung der ersten oder zweiten und der sechsten oder siebenten Rippe ist von Foeten und Säuglingen bei 527 aufeinanderfolgenden Sektionen entfernt und histologisch untersucht worden. Folgende histologische Veränderungen sind gefunden worden: Verbreiterung und grobe Unregelmässigkeit der osteo-chondralen Verbindung, unregelmässige Anordnung der Knorpelzellen an der Ossifikationszone, Vorkommen grosser Mengen osteotiden Gewebes an der Ossificationszone und in der Spongiosa. Alle diese histologischen Veränderungen wurden in allen Gewichts- und Altersgruppen gefunden und zwischen den einzelnen Veränderungen bestand eine deutliche Korrelation. Voll entwickelte histologische Bilder von Rachitis wurden gleichfalls, jedoch selten, in allen Gewichts- und Altersgruppen gefunden, ausgenommen bei den Totgeburten der höchsten Gewichtsgruppe. Das Vorkommen von Fällen mit normalen Befunden war in den höheren Gewichtsgruppen deutlich häufiger

als in den niedrigeren. In 309 Fällen wurde vor der Autopsie eine Röntgenuntersuchung der linken Hand gemacht. Leichte röntgenologische Veränderungen wurden insbesondere bei Foeten von weniger als 300 g Gewicht beobachtet und sie sind bei denen, die histologische Zeichen von Rachitis zeigten, so gut wie bei den anderen gefunden worden. Nichts scheint anzuzeigen, dass die mangelhafte Zufuhr von Vitamin D oder von Mineralien an die gravide Mutter von Bedeutung für die Entwicklung der histologischen Befunde beim Foetus oder Kind ist. Offensichtlich werden die Veränderungen in der Knochenstruktur durch eine Diskrepanz zwischen Knochenwachstum und Mineralisation bewirkt, aber die Ursache dieser Diskrepanz steht zur Diskussion offen.

Característicos hallazgos histológicos raquíticos en fetos y lactantes pequeños.

Las articulaciones osteocondrales de la segunda, tercera y sexta o séptima costillas han sido removidas en fetos y lactantes en 527 autopsias consecutivas y examinadas histologicamente. Se buscaron los siguientes cambios histológicos: ensanchamiento e irregularidad grosera de la articulación osteocondral, alineamiento irregular de las células cartilaginosas en la zona de osificación y presencia de considerable cantidad de osteoide en la zona de osificación y en la esponjosa. Todos estos cambios se encontraron en grupos de todos los pesos y edades, habiendo además pronunciada asociación entre los diferentes alteraciones. Imagen histológica de raquitismo muy desarrollado se encontró también, aunque tenuemente, en todos los grupos excepto en los mortinatos del grupo de mayor peso. La incidencia de casos con hallazgos normales fué significativamente mas alta en los grupos de mayor que en los de menor peso. En 309 casos se practicó examen roentgenológico de la mano izquierda previo a la autopsia. Se observaron ligeras alteraciones roentgenológicos sobre todo en fetos menores de 300 g, tanto en los que presentaron cambios histológicos como en los restantes. Nada sugiere que carencia de vitamina D o poco aporte mineral a la madre embarazada sea de importancia en el desarrollo de cambios histológicos en el feto o lactante. Aparentemente los cambios en la estructura ósea son causados por discrepancia entre el crecimiento óseo y la mineralización, quedando la causa de esta discrepancia abierta a discussión.

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Cortisone Treatment of Idiopathic Pulmonary Hemosiderosis

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Idiopathic pulmonary hemosiderosis (iph) has been diagnosed almost exclusively in children. At the present time about 30 cases are reported. The pathogenesis, however, remains unexplained, and so far no effective way of treatment has been established. Any attempt to clarify the pathogenesis and new therapeutical trials seem therefore worth publication. The following case is reported because of the hematological findings and the experiences in treatment with cortisone.

Wyllie *et al.* collected, in 1948, 17 cases from the literature and added 7 cases of their own. They published an excellent review of the symptomatology of the disease, and in these respects little new has been added.

In most cases the disease runs a typical course with sudden attacks of pallor, dyspnoea, tachycardia, cough and fever. Some patients have abdominal cramps, hemoptyses or blood-streaked sputum, others may have jaundice. In atypical cases there are no distinct attacks, only an increasing pallor and weakness which may also occur in the typical cases between the acute exacerbations. The pulmonary physical signs during the attacks consist of slight dullness, rales and harsh respiratory sounds. Between attacks the findings are insignificant.

The most prominent laboratory findings are a hypochromic anemia, reticulocytosis, positive benzidin reactions in stools and sometimes slightly elevated serum-bilirubin and urobilinuria. X-ray investigations reveal bilateral pulmonary infiltrations which change rapidly in size and distribution.

The prognosis is poor, and the longest survival is 12 years after the onset of symptoms (4).

The pathological changes are limited to the lungs, and in the most advanced cases to the heart as a cor pulmonale. Macroscopically, the lungs have a dark reddish-brown colour, and they appear full and firm. Microscopically, there are intraalveolar and interstitial hemorrhages, large amounts of hemosiderin-laden macrophages, fibrosis and fragmentation and distortion of the elastic fibres in the alveolar and capillary walls. These changes in the

elastic fibres have been considered to be the primary lesion of the disease but similar changes have been found in cases where hemorrhages occurred secondary to mitral stenosis.

Case Report

V. H., a girl aged 22 months, was admitted to the hospital July 9, 1954 as an emergency case because of severe anemia.

The family history was non contributory. She was born at term Sept. 8, 1952 following a normal pregnancy and delivery and there were no neonatal complications. The physical and mental development had been normal, and she had been healthy until the present illness. Her diet was adequate for her age, and there were no feeding difficulties.

In May 54, 2 months prior to admission, she apparently did less well and appeared weak, but the parents did not take notice of it. June 14th she was vaccinated against smallpox and had a moderate local and general reaction. At that time paleness was noticed. She tired easily. The day before admission she was restless, did not play as usual and became increasingly pale. July 8th she had a grunting and heavy respiration and gave the impression of having abdominal pains. In the evening she was still worse, and she was transferred to the Childrens Hospital. Except for a dark stool 2–3 days earlier there had been no signs of external hemorrhages.

On admission to the hospital she was critically ill. The skin was pale and waxy, the respiration frequent and grunting, and she had a slight dry cough. Pulse rate 160. BP not obtainable. Temp. 38.2°. There was dullness over the right side of the chest with bronchial wheezing and a few rales on both sides. Liver and spleen were not palpable, but there was muscular defence below the right costal margin.

Laboratory tests on admission showed Hb 25 %, RBC 1.94 mill., WBC 5200, index 0.66, ESR 36, trombocytes 87,000 and serum-bilirubin 1.5 mg %. Chest X-ray showed bilateral, mottled infiltrations. She was treated with blood transfusions, totaling 870 ml in three days and antibiotics. After 4–5 days the temperature was normalized, the heart rate decreased to 100 and the respiratory rate to 40.

During the next three weeks her general condition was improving, the pulmonary infiltrations decreased and the Hb % stayed about 70 % without transfusions. In the following weeks she had 2 distinct attacks similar to the one on admission with increasing pallor, dyspnoea, tachycardia and slight fever. During these periods the Hb % was falling, the pulmonary infiltrations increased and the benzidine reactions in stools became positive. Fig. 1 depicts the clinical course and main laboratory findings.

Laboratory investigations.

Urine: The urine was physiological except for a pos. Schlesinger reaction in the dilution 1/40 on one occasion. There were normal amounts of coproporphyrin and no uroporphyrin in the urine.

Stools: The benzidine reaction was positive several times, most of them during the attacks, as seen from Fig. 1.

Blood: Hb % 25–90. RBC 2–5 mill. Color index 0.66–0.90. WBC 5–10,000 with normal differential counts. Circulating eosinophils 30–100. Trombocytes 87,000–700,000. Blood groups O MN Rh + (R_1R_2) P −. Coagulation time 1 min. Bleeding time 4 min. Osmotic fragility: Beginning hemolysis 0.44 % NaCl, total hemolysis 0.30 % NaCl. Coagulation

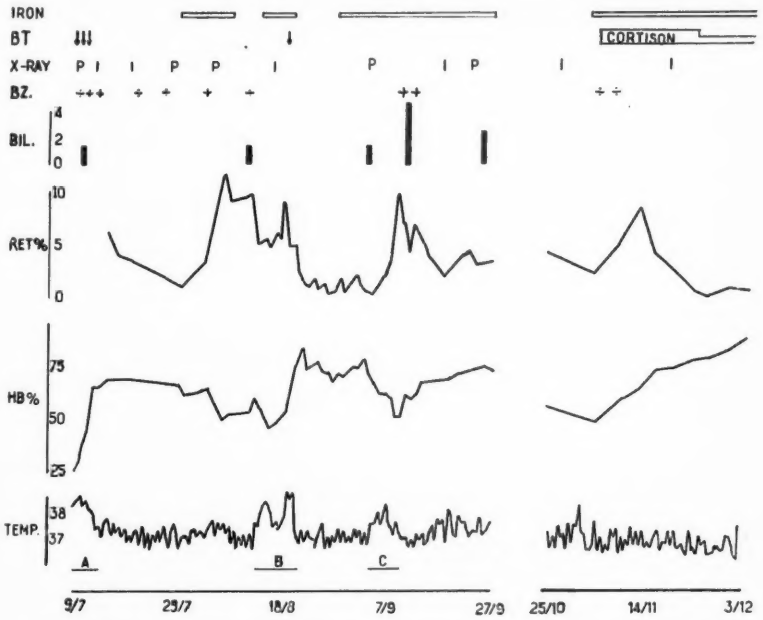

Fig. 1. This figure depicts the clinical course, treatment and main laboratory findings. Abbreviations: Iron = iron therapy. BT = blood transfusions. X-ray = chest X-ray. P = progression in infiltrations. I = improvement. BZ = benzidine reactions in stools. Bil = serum-bilirubin in mg %. Ret % = reticulocytes in per cent. Hb % = hemoglobin per cent. During the periods marked *A*, *B* and *C* the patient had distinct clinical attacks.

investigations: P.P. value 84 %. Proconvertin 66 %. Prothrombin 95 %. Proaccelerin 64 %. Prothrombin-time (Quick's method) 11.8, control 11.5 sec. Serum-bilirubin 1.5–4.75 mg %. Serum iron 22–40 μ %. Total cholesterol: 164 mg/100 ml.

Bone marrow aspirations showed normal hematopoiesis and no pathological elements. Bone marrow sections stained with Turnbulls colour failed to demonstrate any stainable iron on two occasions.

Direct and indirect Coombs' test negative in two specimens. Cold agglutinins: By 4° C titre 4, by 10° C titre 0.

Tourniquet tests negative three times.

Gastric washings: Typical hemosiderin-laden macrophages were demonstrated in large amounts after staining with Turnbulls stain.

X-ray studies: Chest: Bilateral mottled infiltrations which progressed during the attacks and improved rapidly following them. Fig. 1. Intestinal tract: Negative. Skeleton: Negative.

Ophthalmoscopy: Congenital anomalies in the macular region.

Following the third attack of dyspnoea and fever, pulmonary hemorrhages were considered, and a tentative diagnosis of iph was made from the clinical

picture and X-ray findings. This diagnosis was later confirmed by the demonstration of hemosiderin-laden macrophages in the gastric washings.

Splenectomy was considered, but it was decided to try cortisone first Cortisone treatment was started Nov. 5 in doses of 12 ½ mg × 2. From Nov. 23, 1954 the patient was kept on a maintenance dose of 12½ mg daily, per orally.

This treatment was coincident with an improvement in her general condition. The hemoglobin was rising, the reticulocytes were falling after a temporary rise and the chest X-rays were clearing. Dec. 2 she was discharged from the hospital, and the patient has later been followed in the outpatient department. During the follow-up study she was active and well with no signs of pallor or dyspnoea until almost exactly one year after the first symptoms started. At that time the patient had a new attack with dyspnoea and pallor, but not so severe that she could not be up and about, and she recovered in a week without blood transfusions. The hemoglobin which had stayed about 80-90 %, dropped to 53 %, and the reticulocytes increased from previous normal levels (Table 1).

TABLE 1

	20/12 54	27/1 55	29/3 55	25/5 55	11/7 55	3/8 55
Hb %	85	88	95	80	53	80
RBC (mill.) . .	4.68	4.16	4.86	4.88	3.66	4.48
Reticulocytes, %		0.8	0.8	0.6	3.8	1.2
Bilirubin, mg %			1.2	1.5		
Chest, X-ray .	small new infiltration	improved	unchanged	unchanged	unchanged	

Discussion

The pathogenesis of iph is unknown. Ceelen who first described the condition and most of the earlier workers believed that the disease was due to a local capillary defect in the lesser circulation, giving rise to lung hemorrhages. Nancekievill considered hypertension in the pulmonary circulation to be the cause of the hemorrhages. More recently Steiner put forward the theory that iph is an immuno-allergic disease with the lungs as the shock organ. He believes that the disease is caused by an unknown sensitizing agent eliciting autoantibody formation. Antibodies will occur in great quantity in the alveoli of the lungs, and when a fresh allergen is impacted, an allergic reaction takes place giving rise to capillary dilatation, stasis, increase in permeability and bleeding by diapedesis.

The latter theory is at present the most stimulating working hypothesis, and although the suggested sensitizing agents are unknown, the theory points to two different methods of treatment. Splenectomy is one of these and has been performed in 6 cases (1, 3, 11, 14, 17, 18). Cordeiro and Steiner claim that the effect of this procedure is striking, and they strongly advocate this as a routine treatment. In their cases, the attacks did not stop entirely, but they were rarer and much less severe. In one of Wyllie's patients (Case 5), however, a splenectomy did not seem to influence the grave course of the disease.

Treatment with cortisone is the other type of therapy which is logically tried if the theory of an immuno-allergic reaction is accepted. This form of therapy may prove beneficial for two reasons, (1) blocking the allergen-antibody reaction, and (2) preventing the fibrosis of the lungs which is so disabling in the more advanced cases. The present case report describes our experiences with this treatment.

In our patient the treatment with cortisone was coincident with a period during which her condition was improving. There was a rise in hemoglobin, a fall in reticulocytes and an improvement in the X-ray pictures. Originally, the idea was to give cortisone only a short time, but the apparently beneficial effect made us continue the treatment for a longer period. Whether the patient would have had more, or more severe, attacks without hormone therapy is impossible to tell, but because of the rapid improvement and benign course on this therapy, it is the author's opinion that it has been beneficial. This raises the question if a larger cortisone dose could have prevented the last attack in July 55. Because of the dangers of continuous cortisone therapy and the previous good results with splenectomy, the future plan is to perform a splenectomy and combine this with cortisone in intervals when new symptoms arise and for a period afterwards in order to stop the attack and prevent the pulmonary fibrosis.

In evaluating any treatment for a relapsing disease like iph one must be very careful. The previous case reports indicate that there are great variations in the frequency and severity of the attacks, and the time of survival following the first symptoms has varied from a few weeks to 12 years (4). A few case reports of cure following splenectomy must therefore be taken with reservation, but the experiences with this treatment certainly give hope that one can modify the grave course of the disease. Treatment with cortisone has, to the author's knowledge, not been reported previously. The experiences in this case are not conclusive, but they are promising and warrant further trials, maybe combined with splenectomy.

The anemia in iph is of hypochromic type and resembles a post-hemorrhagic anemia. It has, however, some similarities with hemolytic types (jaun-

dice and excessive reticulocytosis), and it is suggested that the anemia has a hemolytic component. The findings of a positive Coombs' test in one case (16) and high cold agglutinin titre in other cases (18) were interpreted in this way.

In the present case the color index was consistently low, the serum-iron between 20–40 μ % and the serum-bilirubin was slightly elevated. On two occasions, bone marrow biopsies stained with Turnbulls stain failed to demonstrate any stainable iron. According to Rath and Finch this is a reliable method to differentiate iron deficiency anemia from hemolytic anemia. In the former none or very little iron is found, in the latter an increased amount of iron can be demonstrated in the bone marrow. The hematological findings in this case indicate that the anemia is due to iron deficiency, probably from blood loss and are in agreement with the findings of Gellis who found low serum-iron and elevated TIBC. Why this and other patients with iph have increased serum-bilirubin and urobilinuria is unknown, but the most likely explanation is that it is due to a combination of increased red cell destruction interstitially and decreased liver function due to liver congestion as a result of impaired circulation through the lungs.

The diagnosis of iph can be made with great certainty from the clinical picture and X-ray findings and may be verified by the demonstration of hemosiderin-laden macrophages in sputum, gastric washings, lung aspiration or lung biopsies. Six different groups of workers (3, 6, 7, 9, 14, 18) have confirmed the diagnosis in this way. Especially in small children it is difficult to obtain sputum, but one should always do several gastric washings before more hazardous procedures such as lung punctures or biopsies are decided upon. In the present case the typical macrophages were found on the second gastric washing.

Summary

A case of idiopathic pulmonary hemosiderosis is reported. The diagnosis was confirmed by the demonstration of typical hemosiderin-laden macrophages in gastric washings. The pathogenesis is discussed, and the theory that iph is an immuno-allergic disease with the lungs as the shock organ is accepted as a working hypothesis. The previous good results with splenectomy are mentioned. In this case treatment with cortisone brought on a period during which the patient's condition was improving, and she remained well on a small maintenance dose for 9 months. At that time she had a new attack, but less severe than the previous attacks, and she recovered without transfusions. The experience with hormone therapy in this case has been promising and warrants further trials, maybe in combination with splenectomy. It is suggested that cortison may prove beneficial for two reasons, (1) blocking an allergen-antibody reaction, and (2) preventing the pulmonary fibrosis.

Traitement par la cortisone de l'hémosidérose pulmonaire idiopathique.

Chez une petite fille de 22 mois présentant une hémosidérose pulmonaire idiopathique a été essayé un traitement par la cortisone. Pendant la durée de l'administration son état fut nettement amélioré, ainsi qu'au cours des 9 mois durant lesquels elle reçut une petite dose d'entretien. A cette date, elle présenta un nouvel accés, moins intense que les précédents, dont elle guérit sans transfusions. Notre expérience de l'hormonothérapie dans ce cas a été assez prometteuse pour justifier de nouveaux essais, peut-être en association avec la splénectomie. L'influence bénéfique du traitement par la cortisone peut s'expliquer de deux manières : 1 — Blocage des réactions antigène-anticorps, et 2 — Prévention de la fibrose pulmonaire.

Cortison-Behandlung bei Idiopathischer Lungen-Haemosiderose.

Bericht eines Falles von idiopathischer Lungen-Haemosiderose bei einem 22 Monate alten Mädchen. Die Behandlung mit Cortison führte eine Phase herbei, während der ihr Zustand sich besserte, was bei einer kleinen Erhaltungsdosis 9 Monate lang anhielt. In dieser Zeit hatte sie eine neue Attacke, aber weniger schwer als die vorigen und sie erholte sich ohne Transfusionen. Die Erfahrung mit Hormontherapie ist in diesem Fall vielversprechend gewesen und rechtfertigt weitere Versuche, vielleicht in Verbindung mit Splenektomie. Es wird angenommen, dass Cortison sich aus zwei Gründen segensreich erweist: 1.) indem es die Allergen-Antikörper-Reaktion blockiert und 2.) indem es die Lungenfibrose verhindert.

Tratamiento con cortisona en hemosiderosis idiopática.

Se comunica el caso de una niña de 22 meses afecta de hemosiderosis pulmonar idiopática. El tratamiento de su afección con cortisona produjo una mejoría que se mantuvo a lo largo de 9 meses con solo una pequeña dosis de mantenimiento. Al cabo de ese lapso tuvo un nuevo ataque, menos severo que los anteriores, del cual se recobró sin necesidad de transfusiones. La experiencia con terapéutica hormonal en este caso fué promisoria e incita a nuevos intentos, quizá en combinación con esplenectomia. Se sugiere, que la acción de la cortisona pudo haber sido benéfica por dos razones: 1) bloqueo de una reacción alergeno-anticuerpo, y 2) prevención de la fibrosis pulmonar.

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Effect of the Fatty Acids of Human Milk and Cow's Milk on Intestinal Lactobacilli

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Introduction

It is generally agreed that the different responses of infants to human milk and cow's milk are based at least partly on the differences in the intestinal flora developed on these diets. The predominating organism in the intestines of infants fed human milk, *Lactobacillus bifidus*, disappears almost totally when infants are transferred to a cow's milk diet and bacteria of other types become dominant instead.

As reported in earlier papers from this laboratory (Roine *et al.*, 1954, 1955), differences in the faeces similar to those typical for infants were also found in rats fed human or cow's milk, respectively. The experiments showed in general that the rat is a suitable test animal for the investigation of several problems of infant feeding. As regards the intestinal flora on the different milk diets, the relative abundance of lactobacilli as compared with other organisms was similar to that in infants. A distinct difference, however, was that L. bifidus was not found in rats, and all the isolates were of the type *Lactobacillus acidophilus*.

Experiments on the nutritional characteristics of L. acidophilus "rat isolates" revealed that in some respects they differed from those of L. bifidus. For example, L. acidophilus did not grow in our ordinary L. bifidus medium (see p. 148), nor in the medium of Teply and Elvehjem used by some authors for the cultivation of L. bifidus. Quite good growth, however, was obtained when the latter medium was supplemented with oleic acid, linoleic acid, or Tween 80 (polyoxyethylensorbitanmono-oleate). For L. bifidus, on the contrary, oleic and linoleic acids proved inhibitory. The "rat lactobacillus" (L. acidophilus) and the "infant lactobacillus" (L. bifidus) thus responded quite differently to the free unsaturated fatty acids *in vitro* whereas *in vivo* human milk and cow's milk, also containing these acids, seem to affect both the bacteria in a similar way.

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Several authors (Tomarelli *et al.*, 1950, Hassinen *et al.*, 1951a, Gyllenberg *et al.*, 1954) have found that certain free fatty acids (lauric and linoleic acids in particular) are strongly inhibitory to L. bifidus. This growth inhibition, however, can be reversed (Tomarelli *et al.*, 1950, Gyllenberg *et al.* 1954). Tomarelli *et al.* conclude that the basis of the different response of infants to human milk and cow's milk is that human milk, as compared to cow's milk, may be a richer source of substances (whey proteins) reversing the effect of the inhibitory acids. Barbero *et al.* also have cited evidence to show that the saturated fatty acids may inhibit L. bifidus *in vivo*. According to them, feeding with cow's milk does not result in a decrease of the L. bifidus count from the intestines of infants if the inhibitory fatty acids are removed from the milk fat before feeding.

There is nothing specific in the literature on the effect of free fatty acids on intestinal L. acidophilus strains. It is reported, however, that certain lactobacilli require free unsaturated fatty acids (e.g. Williams *et al.*). It is noteworthy that Tomarelli *et al.* (1949, 1950) have found that the straight rod type of L. bifidus, which readily develops from the anaerobic branched type upon subcultivation *in vitro*, also requires unsaturated fatty acids as essential nutrients.

According to the data referred to above, it could be supposed that free fatty acids originating from the milk fat may influence the intestinal lactobacilli when they grow in the presence of human or cow's milk. The present investigation was carried out to obtain additional information on the role of free fatty acids in this connection.

Experimental

Methods

The strains of L. acidophilus employed were isolated from the faeces or intestinal contents of milk-fed rats. The isolation was carried out from carrot-liver agar shakes (Garey *et al.*), ordinarily used for counting intestinal lactobacilli. The L. bifidus strains were isolated from faeces of breast-fed infants, employing the medium of Hassinen *et al.* (1951b). The stock cultures of both the test organisms were renewed once a week.

In assays of the effects of different fatty acids, the Teply-Elvehjem medium (abbr. TE-medium) was used as the basal medium for L. acidophilus. Insignificant modifications were made in the amounts of certain vitamins in this medium. The basal medium for L. bifidus (abbr. H-medium) was that proposed by Hassinen *et al.* (1951b), supplemented with tryptic digest of casein or peptonized milk (Difco) as sources of strepogenin, found by us (Gyllenberg *et al.*, 1953a, b) to be essential for some strains of L. bifidus.

Incubation was carried out at 37° C for 48 hours (L. acidophilus) or 72 hours (L. bifidus). A measure of growth was obtained by titration of the acid produced; this was not calibrated against increase in cell mass or turbidity. In the TE-medium L. acidophilus grew very poorly, its acid production corresponding to 0.6–1.6 ml of 0.1*N* NaOH

per 10 ml of medium. L. bifidus in the H-medium, on the other hand, usually produced an amount of acid corresponding to 7.5–9.5 ml of 0.1*N* NaOH per 10 ml of medium.

The fatty acids investigated were added to the media as potassium salts obtained by neutralization of the corresponding acids with KOH in ethanol. The fat of human and cow's milk was separated by centrifugation, and, accordingly, the "fat-fractions" obtained also contained other components; nor were the "skimmed fractions" definitely fat-free. Saponification of the fat fractions was performed with KOH in ethanol. To obtain enzymic digests of milk, digestion with Trypsin, Difco, 1:250, or with Pangestin, Difco, 1:75, were carried out according to the data given in the Difco Manual (9th Ed., 1953).

Effect of Different Fatty Acids on the Growth of L. acidophilus and L. bifidus

In a series of experiments the effect of some saturated and unsaturated fatty acids at different concentrations on L. acidophilus and L. bifidus was tested. The results are given in Table 1. On L. acidophilus, oleic and linoleic acids showed a distinct growth-promoting effect, and myristic and stearic acids were also slightly stimulatory, at least in high concentrations. Propionic, butyric, caproic, and palmitic acids had no effect, whereas capric and lauric acids were inhibitory. As to L. bifidus again, propionic and butyric acids showed no effect, but all the other acids tested were inhibitory.

TABLE 1

Effect of different fatty acids on the growth of *L. acidophilus* (TE-medium) and *L. bifidus* (H-medium). All figures are given in ml of 0.1 *N* NaOH/10 ml of medium minus blank (blanks: TE-medium 0.8 ml; H-medium 9.7 ml).

Addition [1]	Concentration of fatty acids mg/ml									
	L. acidophilus					*L. bifidus*				
	0.2	0.5	1.0	1.5	2.5	0.2	0.5	1.0	1.5	2.5
Propionic acid	0	−0.1	−0.1	−0.1	0	0	0	0	0	+0.2
Butyric acid	−0.1	−0.1	−0.1	0	0	0	0	+0.2	0	0
Caproic acid	+0.1	−0.1	−0.1	−0.1	+0.1	0	0	0	−0.2	−1.9
Capric acid	−0.3	−0.4		−0.6		−7.0	−8.3		−9.5	
Lauric acid	−0.4	−0.5	−0.6	−0.7		−9.3	−9.4	−9.7	−9.7	
Myristic acid	+1.2	+1.4		+1.7		−7.2	−7.9		−8.0	
Palmitic acid	−0.1	0	+0.1	+0.2	0	−4.5	−6.5	−6.5	−6.5	−6.5
Stearic acid	0	0	+0.2	+0.4	+0.9	−4.9	−5.4	−6.3	−6.7	−6.7
Oleic acid	+4.3	+4.8	+5.2	+4.4	+3.9	−4.9	−4.9	−5.1	−5.2	−5.7
Linoleic acid	+3.0	+2.8	+1.9	+1.4	+0.8	−8.4	−8.8	−9.7	−9.7	−9.7

[1] Because of the small amounts of caprylic acid available to the authors, this fatty acid was not tested in these experiments.

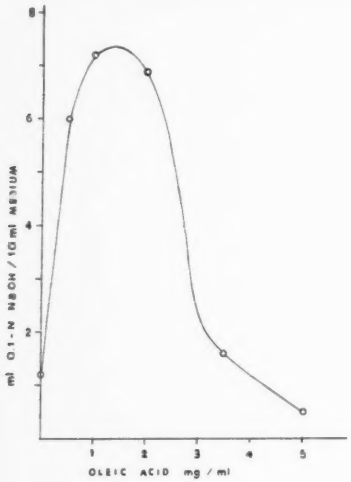

Fig. 1. Effect of oleic acid on the growth of L. acidophilus in the TE-medium.

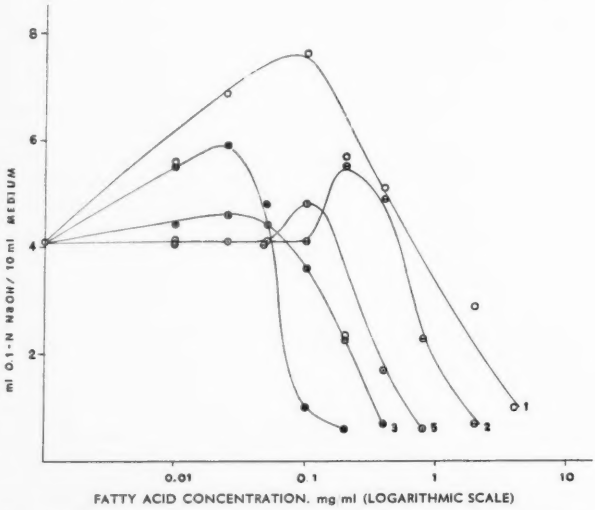

Fig. 2. Effect of caproic (1), caprylic (2), capric (3), lauric (4), and myristic (5) acids on the growth of L. acidophilus (TE-medium containing 1 mg/ml of oleic acid).

Since the growth figures for L. acidophilus in the basal medium were too low to permit an accurate evaluation of the inhibitory effect of capric and lauric acids, larger-scale experiments were performed by employing an addition of 1 mg of oleic acid per ml of the TE-medium. This concentration of

oleic acid had been found optimal for the growth of our strains, as is illustrated in Fig. 1. With increasing concentrations oleic acid turns less effective, and at very high levels even inhibitory. Fig. 2 shows the results of an experiment with some saturated acids tested in the presence of oleic acid. As can be seen all these acids turned inhibitory with increasing concentrations, but with all the acids a stimulatory effect was found just before the inhibiting concentration was reached.

Corresponding experiments with low concentrations of fatty acids were carried out with L. bifidus in the H-medium. As in the previous experiments (Table 1) all the acids tested were inhibitory, and it is noteworthy that the growth-concentration curves always dropped regularly, showing no stimulatory effect of the fatty acids even at low concentrations. This may indicate that the inhibitory fatty acids possibly affect the two organisms in different ways, but this phenomenon was not further investigated.

The critical concentrations were different with different acids, as Table 2 shows. With both organisms the inhibiting effect of saturated acids increases with increasing chain length until lauric acid, but then decreases again. A striking difference between L. acidophilus and L. bifidus exits in the effect of unsaturated acids. Unsaturated fatty acids seem to be essential nutrients for L. acidophilus. For L. bifidus these acids are inhibitory; linoleic acid shows an inhibiting effect equal to that of lauric acid, whereas oleic acid is less effective.

Reversion of the Effect of Inhibitory Fatty Acids

As shown above, oleic and linoleic acids promote the growth of L. acidophilus over a wide range of concentrations, while some saturated fatty acids are strong inhibitors. In natural materials such as milk, components of both these kinds may normally occur. A number of experiments were therefore performed to show to what extent the unsaturated acids may affect the action of the inhibitory saturated acids. The data already given in Fig. 2 and Table 2 indicate that e.g. capric and lauric acids inhibit L. acidophilus even when oleic acid is present in the medium. Fig. 3 shows that oleic and linoleic acids do not reverse the effect of 0.2 mg/ml of lauric acid. Even when they were added in concentrations 20 times that of lauric acid the growth figures of L. acidophilus remained at a quite low level. In this respect Tween 80 was much more effective. Fig. 4 shows, on the other hand, that capric acid had a stimulatory or no effect in concentrations up to 0.3 mg/ml when the medium contained 1 mg/ml of Tween 80. In the same circumstances lauric acid turned inhibitory at about 0.2 mg/ml. Thus Tween 80 at the concentration tested lowered the inhibitory effect of capric and lauric acids, but did not eliminate it completely (cf. Table 2).

TABLE 2

The concentrations of different fatty acids stimulating or inhibiting the growth of *L. acidophilus* (TE-medium containing oleic acid 1 mg/ml) and *L. bifidus* (H-medium). All figures are given in mg/ml.

Fatty acid	Effect					
	Growth promoting		Suppressing		Total inhibition	
	L. a.	L. b.	L. a.	L. b.	L. a.	L. b.
Caproic	0–0.8	0–1.5	0.8 –2.8	> 1.5	> 2.8	(> 2.5)[1]
Caprylic	0–0.5	–	0.5 –1.2	0– > 0.2	> 1.2	(> 0.2)[1]
Capric	0–0.08	–	0.08–0.18	0– 0.2	> 0.18	> 0.2
Lauric	0–0.06	–	0.06–0.08	0– 0.01	> 0.08	> 0.01
Myristic	0–0.15	–	0.15–0.3	0– 0.03	> 0.3	> 0.03
Palmitic		–		0– 0.06		> 0.06
Stearic		–		0– 0.08		> 0.08
Oleic	0–4.0	–	> 4.0	0– 2.5	> 4.0	(> 2.5)[1]
Linoleic	0–3.0	–	> 3.0	0– 0.01	> 3.0	> 0.01

[1] Not tested at higher concentrations.

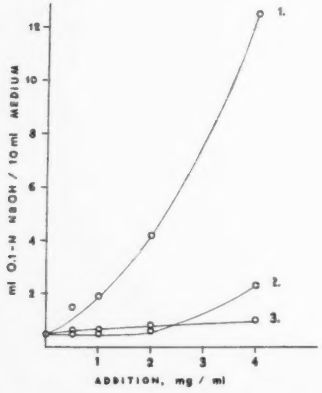

Fig. 3. Effect of oleic (2) and linoleic (3) acids, and Tween 80 (1) on the growth of L. acidophilus in the presence of lauric acid (TE-medium containing 0.2 mg/ml of lauric acid).

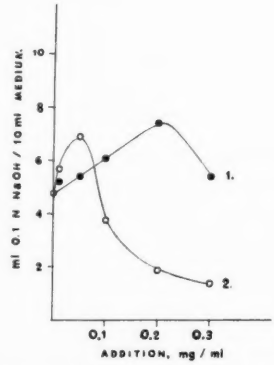

Fig. 4. Effect of capric (1) and lauric (2) acids on the growth of L. acidophilus in the presence of Tween 80 (TE-medium containing 1 mg/ml of Tween 80).

Table 3 shows that Tween 80 causes a decrease in the toxicity of fatty acids for L. bifidus also. The effect of unsaturated acids seems to be more completely reversed than that of saturated acids.

TABLE 3

Effect of Tween 80 on the growth of *L. bifidus* (H-medium) in the presence of free fatty acids. The concentration of capric, lauric, and myristic acids was 1.5 mg/ml, that of the other acids 2.5 mg/ml. Caprylic acid was not tested. All figures are given in ml of 0.1 *N* NaOH/10 ml of medium.

Medium	Without Tween 80	Tween 80 added 2 mg/ml
Basal (H)	9.7	9.6
+ propionic acid	9.7	9.6
+ butyric acid	9.7	9.7
+ caproic acid	7.7	9.4
+ capric acid	0.1	2.9
+ lauric acid	0.0	1.4
+ myristic acid	1.4	5.7
+ palmitic acid	3.1	9.5
+ stearic acid	3.8	9.8
+ oleic acid	4.0	8.0
+ linoleic acid	0.0	6.2

The Effect of Human Milk and Cow's Milk as Sources of Fatty Acids

Additions of human milk or cow's milk to the H-medium caused no changes in the growth figures of L. bifidus, as can be seen from Table 4. As regards the TE-medium and L. acidophilus again, a very pronounced growth promotion was found when human milk was added, whereas the effect of cow's milk remained rather weak (Table 4). It was also interesting to find that the growth-promoting effect of both the milks increased with increasing strength of heat treatment.

TABLE 4

Effect of human milk and cow's milk on the growth of *L. acidophilus* (TE-medium) and *L. bifidus* (H-medium). All figures are given in ml of 0.1 *N* NaOH/10 ml of medium minus blanks. 0.5 ml of milk were added per 10 ml of medium.

Heat treatment of milk	Human milk		Cow's milk	
	L. a.	L. b.	L. a.	L. b.
30 min. at 63°C	7.5		0.9	
2 min. at 100°C	9.3		1.5	
20 min. at 105°C	10.2	0.3	1.7	1.0
20 min. at 120°C	11.6		2.6	
Skimmed milk, 20 min. at 105°C	6.9	0.6	1.8	0.9

TABLE 5

Effect of different milk fractions and caecal contents of milk-fed rats on the growth of *L. acidophilus* (TE-medium) and *L. bifidus* (H-medium). The additions of milk fractions correspond to 0.5 ml milk per 10 ml of medium; 0.5 ml of caecal contents per 10 ml of medium was added. All figures are given in ml of 0.1 *N* NaOH/10 ml of medium.

Addition	*L. acidophilus*		*L. bifidus*	
	Human milk	Cow's milk	Human milk	Cow's milk
Blank	0.9		9.6	
1. Whole milk	9.3	2.4	9.9	10.6
2. Skimmed milk	7.5	2.6	10.2	10.5
3. Fat fraction	5.1	2.0	6.6	7.5
4. Saponified fat	4.2	3.9	0.0	0.0
5. (2) + (4)	14.0	8.2	6.9	9.1
6. Whey		2.8		8.9
7. (4) + (6)		7.5		7.0
8. Caecal content of a milk-fed rat	8.3	8.0	9.7	10.7

On the basis of these results it could be supposed that the difference in effect between human milk and cow's milk arises from the greater amount of free unsaturated fatty acids in the former, and that strong heating produces a further breaking up of unsaturated glycerides. Although no analyses were performed to obtain definite evidence of this assumption, it seems well-founded since it is known that the amount of tri-unsaturated glycerides is distinctly higher in human milk than in cow's milk (Hilditch).

To obtain additional information on the action of fatty acids in milk, several experiments were performed to show the effect of milk fractions, especially that of the fat fraction. Table 5 indicates that upon saponification the effect of the fat fractions of both the milks was almost equal with both L. acidophilus and L. bifidus. On L. bifidus the effect was definitely inhibitory, but with L. acidophilus a slight growth-promotion was found. By combining the saponified fat fractions with the corresponding skimmed milk or whey the inhibitory effect of free fatty acids was nearly completely reversed in the experiments with L. bifidus. This can be ascribed to the detoxifying potency of the milk proteins. In experiments with L. acidophilus again, this recombination gave rise to higher growth figures than those produced by untreated whole milks.

In evaluating this result it must be remembered that on saponification the amounts of both essential (L. acidophilus) and inhibitory fatty acids increase. As was seen in the previous paragraph, very high concentrations

of oleic acid are required to eliminate the inhibitory effect of e.g. lauric acid. Upon saponification, therefore, the inhibitory effect of saturated acids increases, especially since the separation has excluded the detoxifying agents (the proteins). However, when saponified fat was combined with skimmed milk, the detoxifying action of the milk proteins was reintroduced. The greater amount of oleic acid then led to the development of higher growth figures than were found with ordinary untreated milk.

In Table 5 are also presented some data of the effect of the caecal contents of milk-fed rats. These results show that on intestinal digestion cow's milk may become equal to human milk as far as the growth-promotion of L. acidophilus in the TE-medium is concerned. In an otherwise complete medium (H-medium) these additions were equal to ordinary milks in their effect on L. bifidus.

Further evidence of the detoxifying action of milk proteins is presented in Tables 6 and 7. From Table 6 it is obvious that additions of skimmed human milk or skimmed cow's milk have a promoting effect on the growth of L. bifidus in media containing lauric and linoleic acids or saponified human or cow's milk fats.

The growth inhibition caused by linoleic acid seems easier to overcome than that caused by lauric acid, and, in addition, the detoxifying potency of cow's milk seems to be stronger than that of human milk. Corresponding

TABLE 6

Effect of different milk fractions and caecal contents of milk-fed rats on the growth of *L. bifidus* (H-medium) in the presence of inhibitory fatty acids. 0.5 ml of all materials per 10 ml of medium was added. All figures are given in ml of 0.1 *N* NaOH/10 ml of medium.

Medium	Additions						
	None	Skimmed human milk	Tryptic digest of skimmed human milk	Skimmed cow's milk	Tryptic digest of skimmed cow's milk	Caecal content of human milk rat	Caecal content of cow's milk rat
Basal (H)	7.0						
+ lauric acid, 0.2 mg/ml .	0.5	2.5	1.4	4.9	2.8	2.4	2.2
+ linoleic acid, 0.2 mg/ml	0.4	5.0		6.5		5.6	6.4
+ lauric acid, 0.2 mg/ml + oleic acid, 0.5 mg/ml .	0.6	2.6	0.7	5.2	1.9		
+ saponified human milk fat, 0.5 ml/10 ml . . .	0.5	3.2	1.6	4.2			
+ saponified cow's milk fat, 0.5 ml/10 ml . . .	0.7	4.4		6.1	2.1		

TABLE 7

Effect of different milk fractions on the growth of *L. acidophilus* (TE-medium) in the presence of inhibitory fatty acids. 0.5 ml of all materials per 10 ml of medium was added. All figures are given in ml of 0.1 *N* NaOH/10 ml of medium.

Medium	Additions				
	None	Skimmed human milk	Pangestic digest of human milk	Skimmed cow's milk	Pangestic digest of cow's milk
Basal (TE)	0.9				
+ lauric acid, 0.2 mg/ml	0.3	7.8	1.4	3.2	4.0
+ saponified human milk fat, 0.5 ml/10 ml	2.6	11.3	3.1	7.8	
+ saponified cow's milk fat, 0.5 ml/10 ml	2.2	10.5		7.5	4.9

tryptic digests of the milks showed a quite weak detoxifying potency which indicates that the detoxification must be ascribed to intact proteins. The caecal contents of rats fed human milk and cow's milk, respectively, were equally potent in reversing the inhibitory effect of lauric and linoleic acids.

Nearly similar results were obtained with L. acidophilus. Table 7 shows, in conformity with the data given in Table 5, that a simultaneous addition of saponified milk fat and skimmed milk produces a vigorous growth. Moreover, when the medium contained lauric acid, additions of milks produced similar growth figures to those ordinarily obtained in media with no inhibitory agent. Digestion with pangestin resulted in a loss of the detoxifying ability of human milk, but cow's milk turned more potent in this respect than human milk. The process of digestion with pangestin gives rise to lipolysis, besides a breakdown of proteins, and thus additional free fatty acids are introduced. Since cow's milk contains more proteins than human milk, it is probable that the digestion of the cow's milk was incomplete, which may explain the difference in the detoxifying potency of the two digests.

Discussion

In evaluating the results presented above it must be taken into consideration that the "fatty acid effect" on lactobacilli of such an indefinable material as milk obviously depends on (a) the concentration of free growth-promoting acids, (b) the concentration of free inhibitory acids, and (c) the occurrence of substances acting as detoxificants against the inhibitory fatty acids. So far as L. bifidus is concerned the problem is rather simple since the

growth of this organism is not promoted by fatty acids. With L. acidophilus, however, the interpretation of the results is more difficult because of the essential nature of the unsaturated fatty acids for this bacterium.

Our experiments concerned only artificial *in vitro* conditions. Many of the factors involved *in vivo* are almost impossible to take into consideration. The rate of digestion and absorption of fatty and nitrogenous compounds, and the secretion of protein material into the digestive tract may be important factors. So it must be concluded that the influence of free fatty acids on intestinal lactobacilli demonstrable *in vitro* does not provide a good enough basis for assessing the role of these phenomena *in vivo*.

The results of the present study revealed, however, that cow's milk detoxifies the inhibitory fatty acids at least as effectively as does human milk. Upon digestion of milk this ability is decreased, but rather less so with cow's milk. Upon saponification the fat fractions of both milks showed similar effects as inhibitors of the intestinal lactobacilli investigated. Accordingly, it can be supposed that there exist *in vivo* only insignificant differences between the two milks as sources of inhibitory fatty acids, or in the rate of detoxification of these acids. However, certain factors, e.g. the difference in the curdling properties of the milks, may cause decisive differences in the conditions prevailing *in vivo*, and thus influence the amounts of free fatty acids and their detoxification. As is shown in Tables 5 and 6, on the other hand, the caecal contents of rats fed human milk or cow's milk, respectively, were equally potent in reversing the effect of inhibitory fatty acids.

As a source of the unsaturated fatty acids essential for L. acidophilus, human milk (skimmed human milk, the fat fraction of human milk) is distinctly more beneficial than cow's milk. Upon saponification of the fat fractions cow's milk showed, however, an equal potency. When saponified fat fractions were recombined with skimmed milk, the difference in potency between human milk and cow's milk was less pronounced than that found with ordinary milks, and this difference disappeared completely if the saponified fat fractions were combined with enzymic digests of skimmed milks. In addition, the caecal contents of rats fed human or cow's milk possessed an equal potency to promote the growth of L. acidophilus. So it can be concluded that both the milks *in vivo* may be equally potent sources of the fatty acids promoting the growth of L. acidophilus.

Our results of the effect of human milk and cow's milk on L. acidophilus agree in most respects with the data of Tomarelli *et al.* (1949, 1950) as regards the straight rod type of L. bifidus. This similarity in behaviour of the straight rod L. bifidus and L. acidophilus is interesting since it indicates that these organisms are physiologically closely related. L. bifidus changes

readily to the straight rod type when subcultivated *in vitro*, and upon this change both the organisms thus show very similar properties. Accordingly it can be supposed, although definite evidence in this respect may be difficult to obtain, that *in vivo* also they possess similar features. At any rate the "rat lactobacillus" is related to the "human lactobacillus", and this fact provides additional evidence to show that rats are well suited as test animals when problems connected with milk formularies for young infants are studied.

Summary

When cultivated *in vitro* the main intestinal lactobacillus of infants, *Lactobacillus bifidus*, and that occurring in the intestines of milk-fed rats, *Lactobacillus acidophilus*, are influenced in different ways by free fatty acids. Apart from some short-chain saturated acids, saturated and unsaturated fatty acids inhibit the growth of L. bifidus. L. acidophilus is inhibited by saturated fatty acids, but requires unsaturated acids as essential nutrients.

When intestinal lactobacilli grow in the presence of milk, the milk fat is a source of fatty acids; but, on the other hand, the proteins of milk act as detoxificants of inhibitory fatty acids. Human milk may contain a greater amount of free unsaturated fatty acids than cow's milk, and accordingly human milk promotes the growth of L. acidophilus more strongly than cow's milk. However, because of the action of proteins ordinary milks show no inhibitory "fatty acid effect" on intestinal lactobacilli. Separated and saponified fat fractions of both milks, on the other hand, are strongly inhibitory to L. bifidus, but slightly stimulatory to L. acidophilus. Upon enzymic digestion both the milks sligthly reverse the action of inhibitory fatty acids and also that of saponified milk fat. In this respect digests of cow's milk are at least equally potent as digests of human milk.

On the basis of these results it can be supposed that *in vivo* human milk and cow's milk show a similar effect on the intestinal lactobacilli both as sources of inhibitory or stimulatory fatty acids and as sources of substances able to detoxify the inhibitory fatty acids.

Effets des acides gras des laits de femme et de vache sur les bacilles lactiques intestinaux.

Lorsque l'on cultive, in vitro, le plus important bacille lactique existant chez les enfants, le *Lactobacillus bifidus*, et lorsqu'on observe le comportement du *Lactobacillus acidophilus* dans l'intestin de rats soumis à un régime lacté, on remarque qu'ils sont influencés de diverses manières par la présence d'acides gras à l'état libre. Les acides gras saturés et non saturés, exception faite pour quelques acides saturés à courte chaine, empèchent le développement du *L. bifidus*. Le développement du *L. acidophilus* est inhibée uniquement par les acides gras saturés et ce dernier exige, au contraire, la présence d'acides gras non saturés qui sont nécessaires à son métabolisme. Lorsque le développement des bacilles lactiques intestinaux se fait en présence de lait, la graisse de ce lait est une source d'acides gras, mais, d'un autre coté, les protéines de ce lait agissent comme antagonistes des acides gras inhibiteurs. Le lait de femme peut contenir une plus grande quantité d'acides gras non saturés à l'état libre que le lait de vache et, de ce fait, il est plus favorable au développement du *L. acidophilus* que le lait de vache. Cependant, à cause de l'action des protéines, le lait ordinaire ne montre aucunement

l'effet inhibiteur des acides gras sur les bacilles lactiques intestinaux. D'autre part, les fractions séparées et saponifiées des graisses de ces deux laits sont fortement inhibitrices pour le *L. bifidus* mais faiblement stimulatrices pour le *L. acidophilus*. Après une digestion enzymatique les deux laits renversent faiblement l'action des acides gras inhibiteurs de même que celle de la graisse de lait saponifiée. A cet égard, les produits de digestion du lait de vache ont, au minimum, le même pouvoir que ceux du lait de femme. Sur la base des ces résultats, on peut supposer que, in vivo, le lait de femme et celui de vache ont un effet similaire sur les bacilles lactique intestinaux, tous deux étant la source d'acides gras stimulateurs et inhibiteurs et étant tous les deux, également, la source de substance capables de neutraliser les acides gras inhibiteurs.

Über die Wirkung der Fettsäuren der Frauen- und Kuhmilch auf die intestinalen Lactobazillen.

Bei Züchtung in vitro werden der wichtigste intestinale Lactobazillus der Säuglinge, *Lactobacillus bifidus*, und der bei mit Milch ernährten Ratten vorkommende, *Lactobacillus acidophilus*, in verschiedener Weise von freien Fettsäuren beeinflusst. Abgesehen von einigen kurzkettigen gesättigten Säuren hemmen gesättigte und ungesättigte Fettsäuren das Wachstum von *L. bifidus*. *L. acidophilus* wird durch gesättigte Fettsäuren gehemmt, erfordert jedoch ungesättigte Säuren als essentiellen Nährboden. Wenn intestinale Lactobazillen in Gegenwart von Milch wachsen, ist das Milchfett eine Quelle für Fettsäuren, aber andererseits wirken die Milchproteine als Entgifter auf inhibitorische Fettsäuren. Frauenmilch dürfte einen höheren Gehalt an freien ungesättigten Fettsäuren als Kuhmilch haben und demgemäss fördert Frauenmilch das Wachstum von *L. acidophilus* stärker als Kuhmilch. Jedoch zeigen gewöhnliche Milcharten wegen der Wirkung der Proteine keinen hemmenden „Fettsäureeffekt" auf intestinale Lactobazillen. Isolierte und verseifte Fettfraktionen beider Milcharten wirken stark hemmend auf *L. bifidus*, aber leicht fördernd auf *L. acidophilus*. Unter enzymatischer Verdauung kehren beide Milcharten die Wirkung der inhibitorischen Fettsäuren und ebenfalls des verseiften Milchfettes um. In dieser Hinsicht sind Digestionsprodukte von Kuhmilch mindestens ebenso wirksam wie die von Frauenmilch. Auf Grund dieser Resultate kann angenommen werden, dass in vivo Frauenmilch und Kuhmilch einen ähnlichen Effekt auf die intestinalen Lactobazillen zeigen, sowohl als Quelle von hemmenden wie fördernden Fettsäuren und als Quelle von Substanzen, die in der Lage sind, die inhibitorischen Fettsäuren zu entgiften.

Efecto de los ácidos grasos de las leches humana y vaca sobre los lactobacilos intestinales.

Cuando el *Lactobacillus bífidus*, principal lactobacilo del lactante, y el *Lactobacillus acidophilus*, presente en el intestino de ratas alimentadas con leche, se cultivan in vitro, son influenciados de diferente modo por ácidos grasos libres. Los acidos grasos, saturados e insaturados, inhiben el crecimiento del *L. bífidus*, salvo algunos ácidos saturados de cadena corta. El *L. acidophilus* es inhibido por ácidos grasos saturados pero requiere los insaturados como nutrición esencial. Cuando los lactobacilos intestinales crecen en presencia de leche, la grasa de esta es la fuente de ácidos grasos. Por otra parte, las proteínas de la leche actúan como detoxificante de ácidos grasos inhibitorios. La leche humana puede contener mayor cantidad de ácidos grasos insaturados que la leche de vaca, promoviendo por lo tanto un mayor crecimiento que esta. Sin embargo, debido a la acción de las proteínas, las leches corrientes no muestran "efecto ácido-graso" sobre los lactobacilos intestinales. Fracciones grasas separadas y saponificadas de ambas leches son fuertemente inhibitorias del *L. bífidus* pero débilmente

estimulantes del *L. acidophilus*. En cuanto a digestión enzimática, ambas leches in vierten ligeramente la acción de ácidos grasos inhibitorios y también la de la gras saponificada. Este tipo de digestión es igualmente potente sobre las leches de vaca humanas. Sobre estas bases se puede asumir que in vivo, la leche humana y la de vac muestran efectos similares sobre los lactobacilos intestinales como fuente de ácido grasos estimulantes e inhibitorios y de sustancias capaces de detoxificar los ácido grasos inhibitorios.

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Addendum

After the manuscript had been sent to press, F. Petuely reported (personal communication) that L. bifidus is demonstrable in rats fed certain "bifidogenic" diets. Our own recent observations have confirmed this finding. We have found, however, that even under these conditions other lactobacilli (L. acidophilus) predominate, thus evidently determining the general behaviour of lactobacilli in the intestines of milk-fed rats. This question will be discussed later in more detail.

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From the Pediatric Clinic (Chief: Professor ALFRED SUNDAL, M.D.) and the Department of Bacteriology and Serology, the Gade Institute (Chief: Professor TH. M. VOGELSANG, M.D.), University of Bergen, Norway

Third-Generation Syphilis in an Infant with Sero-Tests Indicating Passively Transferred Maternal Reagins

by ALFRED SUNDAL and TH. M. VOGELSANG

It is impossible from the positive syphilitic tests in a newborn infant definitely to ascertain if (1) the reagins are derived from passively transferred antibodies from the woman to the fetus giving a non-syphilitic infant or (2) the reagins originate from an active syphilitic infection of the fetus with consequent prenatal syphilis of the infant at birth. Repeated serological, clinical and X-ray controls are necessary through the first year of life to make a correct diagnosis. But with this rule in mind some suggestions can be made from the situation at birth.

In a previous report Vogelsang & Sundal have come to the following conclusion: If a syphilitic woman treated adequately with penicillin during pregnancy still has positive sero-tests, the Meinicke test included, at the time of delivery, and if the newborn infant has positive complement fixation tests and/or VDRL ("Venereal Disease Research Laboratory" test), but a negative Meinicke test, these findings should indicate that the infant is not syphilitic but still possesses passively transferred maternal reagins.

Passively transferred reagins will diminish in the first few weeks of life. In a series of 25 infants born of syphilitic women with sero-positive syphilitic tests in the newborn, the passively transferred reagins from the woman to the non-syphilitic fetus gave moderate positive complement fixation tests and/or VDRL in the newborn, and the sero-positivity did not last for a longer time than maximum eight weeks. But also in prenatal syphilis a fall in the titres of the syphilitic reactions may be noted in the time following birth. In 39 cases of prenatal syphilis Nörgaard has shown that in one-third of the cases a spontaneous fall in the reagins took place after birth. In prenatal syphilis a fall in the sero-positivity may revert to sero-negativity.

In some cases the newborn infant may have negative serological tests and still have prenatal syphilis. Nörgaard has thus described a prenatal syphilitic infant with sero-negativity 67 days after birth and positive tests when 130 days old. Nyhus has also described three cases with negative syphi-

TABLE 1

The serological tests for syphilis in mother and infant.

Tests	Mother	Infant born April 12, 1953. Results: Date and age											
	Results at delivery	24/4 53 12 days	4/5 53 22 days	7/5 53 25 days	14/5 53 1 month	27/5 53 1½ month	5/6 53 2 months	16/6 53 2 months	17/7 53 3 months	21/8 53 4½ months	22/9 53 5½ months	22/1 54 9 months	22/4 54 1 year
1	12	0	12	5	N	N	N	N	N	N	N	N	N
2	12	P	10	5	N	N	N	N	N	N	N	N	N
3	8	0	8	N	N	N	N	N	N	N	N	N	N
4	P	N	N	N	N	N	N	N	N	N	N	N	N
5	P	P	WP	WP	N	N	N	N	N	N	N	N	N

↑ 9/5 53 Penicillin treatment started

↑ 12/5 53 Spinal fluid N

Symbols for the tests:

1. Complement fixation test carried out with crude antigen.
2. Complement fixation test carried out with cardiolipin antigen.
3. Complement fixation test carried out with sitolipin antigen.
4. Meinicke clarification test.
5. VDRL tube flocculation test.

Numbers—Titres in units in the quantitative tests corresponding approximately to the log of the dilution titres (Vogelsang 1952/53)

P—Positive

WP—Weakly positive

N—Negative

0—Not performed because of lack of serum

Fig. 1. Eleven days old. Destructive lesions in the medial part of the left femur neck.

litic tests in infancy but with clinical and X-ray signs indicating prenatal syphilis, and cured by antisyphilitic treatment. Syphilis was diagnosed in two cases when the children were 10 days old, and in one child at an age of 10 months.

The reports indicate that a systematic follow-up is necessary for all infants born of syphilitic mothers, whether the women are antisyphilitic treated or not. The examinations of the infant must comprise repeated serological, clinical and X-ray controls at short intervals during the first year of life.

In a survey of clinical, X-ray and serological studies of infants born of syphilitic women, one of the 26 newborn showed prenatal syphilis with such deviation from the common findings in prenatal syphilis that the case should be published.

Case Report

The child was born at term of a primipara 21 years of age. The child's grandmother had prenatal syphilis. She gave birth to four children, two of whom with prenatal syphilis. One of these women with prenatal syphilis was the mother of the child in question. Its mother was given a course of neosalvarsan and bismuth treatment 11 years old,

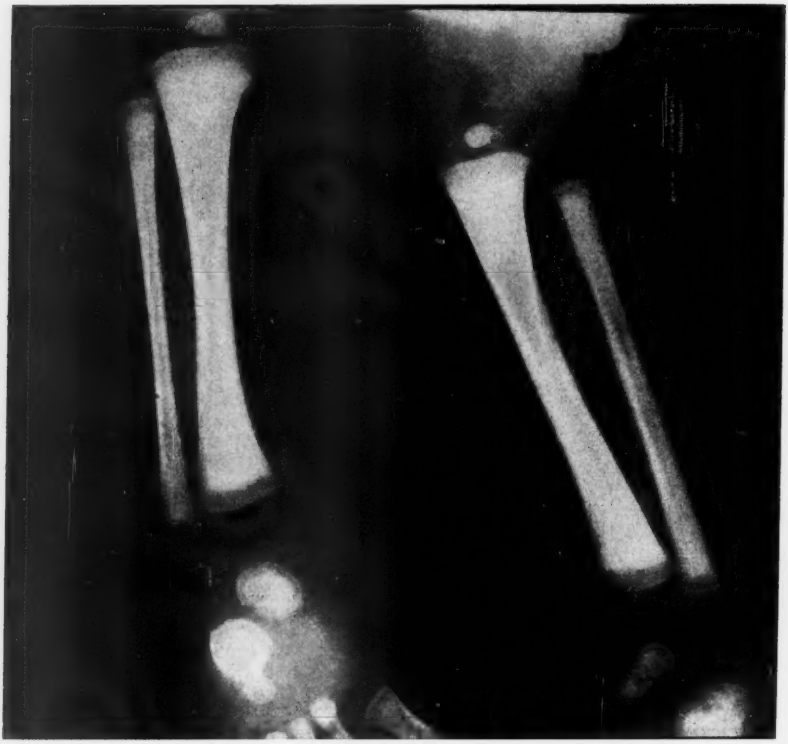

Fig. 2. Twenty-five days old. A band shadow of diminished density in the juxta-epiphyseal end of the shaft—syphilitic metaphysitis.

but later, until the birth of her first child, she neither got any treatment nor was controlled. A routine blood-test for syphilis was taken just before delivery and showed positivity (Table 1).

The first clinical symptoms in the child were noticed when he was nine days old. The upper part of the left femur now showed swelling, and movement of the left leg was painful. Fifteen days old, the boy with birthweight 2950 g and length 49 cm, was transferred to the Pediatric University Clinic. The left leg was now fixed with slight flexion and abduction in the hip joint. In the left trochanteric region there was considerable swelling of the bony parts of the femur, while skin and subcutis were normal. The child had no coryza, no rash, no enlargements of liver or spleen. The hemoglobin, the number of red and white blood corpuscles, the differential leucocyte count and the sedimentation rate were all normal.

Eleven days old, the X-ray examination showed destructive processes in the medial part of the left femur neck and lateral dislocation of the caput femoris (Fig. 1). An X-ray examination of the whole skeleton showed also changes in all long bones: a band shadow of diminished density in the juxta-epiphyseal end of the shaft—as seen in syphilitic

Fig. 3. Thirty-two days old. Destruction of the proximal end of the left femur with periosteal reaction. Now also destructive lesions in the right femur neck. Diminished density zone in the periphery of the pelvic bones.

metaphysitis (Fig. 2). There was no periosteal thickening. Repeated X-ray controls at the age of 32 days showed increasing destruction of the left caput and collum femoris with periosteal reaction, now also an incipient process in the trochanter minor region of the right femur. The signs of systemic syphilitic inflammation in the bones had increased, the zone of diminished density near the joint ends of the long bones being broader. These X-ray manifestations were now not only limited to the long bones but also to the cuboide bones in the feet and to the flat bones such as os ileum. In all the bones there was a transverse striping of the metaphysis (Fig. 3).

Table 1 shows the sero-tests for syphilis in mother and infant. In the mother, untreated for the last 10 years and also getting no treatment during pregnancy, all the reactions, both the complement fixation tests and the two flocculation tests, were definitely positive. In the infant two to three weeks old the complement fixation tests were positive up to the same titres as in the mother at delivery, VDRL was weakly positive, but the Meinicke reaction was negative and remained so during the whole observation period. In the further serological examinations of the infant the quantitative complement fixation tests showed diminished values, and when 31 days old all the syphilitic tests were completely negative. By the way, the diagnosis of prenatal syphilis was confirmed from the X-ray examinations, and a course of penicillin therapy was instituted with 120,000 units each day through 10 days from an age of the infant of 27 to 37 days. By repeated controls the sero-tests always remained negative during one year. The generalized syphilitic metaphysitis soon cleared up without relapses, the left leg leaving a destructive upper part of the femur with luxation of the left hip. Otherwise the infant was in good health without any skin or visceral manifestations of prenatal syphilis.

Discussion

In this case the mother had at delivery both positive complement fixation tests and flocculation tests. Quantitative complement fixation tests in the infant's serum were first performed when he was 22 days old. The titres of the infant's serum corresponded fairly well to the titres of the mother's serum at delivery, VDRL was weakly positive, but the Meinicke reaction was negative. During the next few days the positive sero-tests decreased and after the infant was 31 days old all serological tests were completely negative on the further controls during the first year of life.

These serological results are in good conformity with what is usually found when the mother's reagins are passively transferred to the fetus. Four days before all the tests had reverted to sero-negativity a penicillin therapy was instituted, but this interval was too short to have had any influence on the sero-tests. Meanwhile, when the infant was 9 days old, the first clinical symptoms were noted and X-ray examinations showed generalized syphilitic metaphysitis in progress. It is generally accepted that an active syphilitic infection in progress, acquired or prenatal, will give rise to positive serological tests, but in the present case there was a reversal to sero-negativity within the first month of the infant's life.

Both the boy's grandmother and his mother were born with prenatal syphilis. His mother was given antisyphilitic treatment when she was 11 years old, 10 years before the delivery. When the treatment was finished, she still had unchanged positive sero-tests. Such sero-resistance is a usual finding in late prenatal syphilis. Even within five years of treatment, it is only on infrequent occasions that there is a reversal to sero-negativity (Rein & Kostant). In the present case, the woman was given an inadequate treatment consisting of only one short course of neosalvarsan and bismuth. Later she had no serological examinations before delivery. It is therefore now impossible to ascertain when her infection again became active.

There are different ways of determining when the fetus becomes infected *in utero*. Since the depth of the syphilitic process in the bones at birth is a reasonably accurate index of its duration, an X-ray examination of the long bones soon after birth will give good information. Such studies have indicated that the fetus is not infected before the sixteenth or twentieth week. Such studies suggest that in many instances the fetus is not infected until very late in pregnancy. It is possible that as many as 60–70 per cent of the infants with prenatal syphilis are not infected until the last two months of pregnancy (Ingraham).

Eleven days old, an X-ray examination of the whole skeleton was carried out. It showed a syphilitic metaphysitis of the long bones, but no periosteal thickening. These findings suggest that the syphilitic infection was still in an early stage and may be in accordance with the serological results.

When the infant was born the infection was still so young that there had been no sufficient time for the infant to develop its own antibodies. The passively transferred maternal reagins reverted in the usual way to sero-negativity within one month after birth. At this time, before the infant had developed its own serologically demonstrable antibodies, a course of penicillin therapy was instituted. The syphilitic metaphysitis soon cleared up and on repeated serological controls during one year the sero-tests remained negative. This rapid restoration also suggests that the fetus must have been infected late in pregnancy. The response to penicillin therapy is mostly related to the duration of the infection. As the infant had been recently infected it responded readily to the treatment.

Several cases of prenatal syphilis are reported with negative sero-tests at delivery. It is probable that such cases are infected late in pregnancy and may first develop positive serological reactions at variable times after delivery. If the woman has been given antisyphilitic treatment during pregnancy, it is also possible that the infant may have had an active syphilitic infection *in utero*. Following penicillin therapy during pregnancy, the infant may be born with negative sero-tests or with passively transferred maternal reagins,

but it is not certain that the syphilitic process is cured. It may be latent and the infant may later develop a serological and clinical relapse. The negative results at delivery will only reflect the serological status of the newborn at that particular time. It is therefore necessary to follow up all infants born of syphilitic mothers, treated or untreated. Repeated clinical and quantitative serological examinations during the first year of life are a *sine qua non*.

Summary and Conclusion

A case of third-generation syphilis is reported. Although the newborn infant had a generalized syphilitic metaphysitis in progress, the serological tests indicated passively transferred maternal reagins which reverted to sero-negativity in the usual way within one month after delivery.

These serological deviations from the common findings in prenatal syphilis are discussed. It is suggested that the infant was infected so late in pregnancy that at delivery he had not yet developed his own antibodies. The serological findings at delivery will only reflect the serological status of the newborn at that particular time. It is therefore necessary to follow up all infants born of syphilitic women, treated or untreated.

Syphilis de troisième génération chez un nourrisson dont les tests sérologiques mettaient en évidence des réagines maternelles transmises passivement.

Observation de syphilis de troisième génération. Bien que le nourrisson soit porteur de lésions métaphysaires syphilitiques généralisées et évolutives, les épreuves sérologiques ont mis en évidence des réagines maternelles transmises passivement et les examens sérologiques sont devenus négatifs, comme d'habitude, dans le mois qui suivit la naissance. Discussion des variations sérologiques prénatales, par rapport aux cas habituels. Il est suggéré que le nourrisson a été infecté si tard, dans la grossesse, qu'il n'avait pas encore fourni ses propres anticorps au moment de la naissance. Les résultats de l'examen sérologique à la naissance ne font que réflèter l'état sérologique du nouveau-né à ce moment particulier. Il faut donc suivre l'évolution de tous les enfants de mères syphilitiques traitées ou non.

Syphilis in dritter Generation bei einem Säugling, dessen serologische Befunde einen passiven Übergang mütterlicher Reagine anzeigen.

Es wird von einem Fall von Syphilis in dritter Generation berichtet. Obgleich das Neugeborene eine generalisierte syphilitische Metaphysitis hatte, zeigten die serologischen Befunde passiv übertragene mütterliche Reagine, die in der üblichen Weise innerhalb eines Monats nach der Geburt in Seronegativität umschlugen. Dieses serologische Abweichen von den üblichen Befunden bei foetaler Syphilis wird erörtert. Es wird angenommen, dass das Kind so spät in der Schwangerschaft infiziert wurde, dass es bei Geburt noch nicht seine eigenen Antikörper gebildet hatte. Die serologischen Befunde bei der Geburt geben lediglich Auskunft über den serologischen Status des Neugeborenen zu diesem speziellen Zeitpunkt. Es ist deshalb notwendig, alle von syphilitischen Müttern geborenen Kinder, ob behandelt oder unbehandelt, weiter zu verfolgen.

Sífilis en tercera generación. Lactante con reacciones serológicas indicando transferencia pasiva de reaginas maternas.

Se presenta un caso de sífilis en tercera generación. Aunque el recién nacido presentó metafisitis generalizada en actividad, las reacciones serológicas indicaban reaginas maternas transferidas pasivamente que viraron hacia la negatividad alrededor del mes de edad. Se discute este hallazgo serológico poco común en sífilis prenatal sugiriendo que el lactante se haya infectado en las últimas etapas del embarazo no habiendo todavía desarrollado sus propios anticuerpos en el momento del parto. Los hallazgos al nacer reflejarían solamente el estado serológico en ese momento siendo por lo tanto necesario estudiar y controlar posteriormente todos los lactantes nacidos de madres sifilíticas, sean estas tratadas o no.

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Hypothyroid Signs in Encephalopathy

by M. d' AVIGNON and R. ZETTERSTRÖM

Retarded mental development, low basal metabolism and abnormal bone age are symptoms regularly encountered in congenital hypothyroidism. However, the diagnosis of congenital hypothyroidism cannot be established on these symptoms alone. More direct evidence of a low or lacking thyroid activity such as the typical myxoedematous appearance or low serum protein bound iodine level and low uptake of radioiodine over the thyroid gland is also required. In this communication this statement will be illustrated by the clinical description and investigation of three severely brain damaged children who exhibited some of the features characteristic of hypothyroidism, despite normal thyroid function.

Methods of Investigation

The total number of ossification centers was determined roentgenologically according to the method of Elgenmark (1) and the basal metabolic rate (BMR) by Karlberg's (2) method. The 24-hour thyroid uptake of radioiodine and the urinary excretion of the isotope were measured after an oral dose of 10–20 microC of carrier free I^{131}. One month later the response of the thyroid gland to stimulation with thyrotropic hormone (TSH) was tested in two of the patients. 7.5 mg of TSH were given intra-muscularly daily for three days and the effect on I^{131} uptake of the thyroid gland was studied. The serum protein-bound iodine level (PBI) was determined according to Baker (3).

Case Reports

Case 1.—K. S., a 13 month old girl was admitted because of mental retardation and suspicion of hypothyroidism. The pregnancy and delivery had been normal. The mother had noticed that the child was mentally retarded when she approached the age of 4–5 months. The physical examination revealed a drowsy, severely hypotonic and retarded child. She was slightly malnourished and her weight was 8770 g. No signs of myxoedema were noted. (Fig. 1.) Very probably the girl was blind but there were no significant abnormalities on ophthalmologic examination. The intelligence quotient was below 0.3.

The skull was rather large and the head circumference was 49 cm. EEG-examination did not reveal any definite abnormalities. The cause of the encephalopathy remained unknown. Special investigations are listed in Tables 1 and 2.

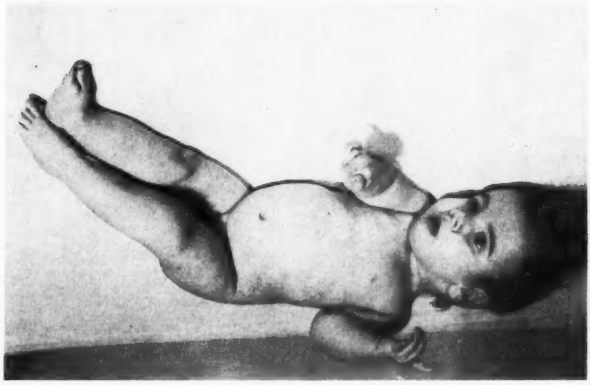

Fig. 1.

Fig. 2.

Case 2.—T. B., was an illegitimate boy. Pregnancy and delivery were normal. There was no history of asphyxia. Mental retardation was observed in early infancy and intellectual development was very slow. On admission at the age of 17 months the boy was not able to sit without support. He had no signs of myxoedema. (Fig. 2.) The skull was rather short but high with a circumference of 43.5 cm. Serum cholesterol was 200 mg %. EEG did not reveal any definite abnormalities. For special investigations, cf. Tables 1 and 2.

Fig. 3.

TABLE 1

Clinical and biochemical findings.

	Age	Basal metabolic rate %	Bone center development	Serum cholesterol level mg/100 ml	Serum carotine level μg/100 ml
Case 1.	13 months	−25	6 (normal for age 25±9. For length 19±5)	176	not determined
Case 2.	17 months	−27	13 (normal for age 24±8. For length 25±7)	200	not determined
Case 3.	13 months	−33	18 (normal for age 29±9. For length 29±8)	224	410

Case 3.—M. B., a girl was born after normal pregnancy, delivery was uneventful and there was no history of asphyxia, but the child was rather drowsy during the first 10 days of life, later became normal. Physiologic neonatal jaundice persisted for about 3 weeks and then disappeared completely. General mental retardation was obvious already during the first months of life. The mother was aware of this mental retarda-

TABLE 2

Functional tests of the thyroid gland.

	Serum protein-bound iodine level mg/100 mg	24-hour thyroid uptake of I 131, per cent of dose	24-hour urinary output of I 131, per cent of dose	24-hour thyroid uptake of I 131 after treatment with TSH, per cent of dose
Case 1.	not determined	24	40	not determined
Case 2.	7.5	15	not determined	32
Case 3.	8.0	18	63	46

tion, but the child was brought to the clinic first at the age of 13 months because of generalized epileptic seizures. There were no external signs of myxoedema. (Fig. 3.) The child was drowsy, hypotonic and mentally retarded. The skin was slightly yellow. The head circumference was 47 cm. The pneumoencephalogram revealed atrophy of the brain and the EEG was pathological with slow dysrythmia and spiky potentials. Serum cholesterol level was 224 mg % and the serum contained 410 μg of carotinoids per 100 ml. For special investigations see Tables 1 and 2.

Discussion

All three cases thus showed some similarities to congenital hypothyroidism: they all were mentally retarded, their skeletal development was delayed and the basal metabolism showed values usually encountered in hypothyroidism. On the other hand the patients differed in many important points from congenitally hypothyroid children. No external signs of myxoedema were noticeable and PBI values were within normal limits. The 24 hour uptake of I^{131} by the thyroid gland varied between 15 and 24 per cent of the administered dose. (In our clinic corresponding figures in euthyroid children range from 15–20 per cent upwards, and in known cases of congenital hypothyroidism the values were all below 10 per cent.) Treatment with thyroid hormone had no effect on basal metabolism. A secondary pituitary hypothyroidism which might be suggested from the pronounced response to stimulation with TSH (cf. Pickering and Miller) could not exist in the presence of a normal PBI. Pituitary or suprarenal failure were further excluded by the clinical investigations, the normal ACTH test and the normal urinary 17-ketosteroid excretion. Thyroid hormone treatment also decreased the I^{131} uptake of the thyroid gland—another sign suggesting normal pituitary function. All these facts speak in favour of normal thyroid activity.

One very important similarity is present in all three cases: they were all brain damaged and were considerably mentally retarded, having an I.Q. of about 0.3. Case 1 had a slightly enlarged head, Case 2 was microcephalic, and Case 3 had epileptic seizures and pneumoencephalography revealed brain atrophy.

Conclusions

It would be difficult to draw any definite conclusions from these cases, but the brain damage and the signs suggesting hypothyroidism may be related.

The authors want to point to the need for complete clinical investigations in patients whose diagnoses of congenital hypothyroidism is not absolutely unequivocal clear.

Summary

Three severely brain damaged children of an age between 13 and 17 months were found to have retarded bone center development and low basal metabolic rate. The absence of myxoedematous appearance suggested that these symptoms were not attributable to an abnormal thyroid gland activity. Studies of iodine metabolism demonstrated normal thyroid function. It is concluded that atypical cases of congenital hypothyroidism should be investigated completely.

Signes d'hypothyroïdie au cours d'encéphalopathie.

Chez trois enfants atteints de lésion cérébrale grave et âgés de 13 à 17 mois, existait un retard d'apparition des points d'ossification et un abaissement du métabolisme de base. En l'absence de signes de myxœdème, ces symptômes ne furent pas attribués à une anomalie de la fonction thyroïdienne. L'étude du métabolisme de l'iode montre que cette fonction était normale. L'auteur conclut que les cas d'hypothyroïdie congénitale atypique doivent être étudiés d'une manière complète.

Hypothyreotische Zeichen bei Encephalopathie.

Bei drei schwer hirngeschädigten Kindern im Alter von 13–17 Monaten wurde eine verzögerte Knochenkernentwicklung und ein niedriger Grundumsatz gefunden. Die Abwesenheit eines myödematösen Erscheinungsbildes deutete darauf hin, dass diese Symptome nicht einer gestörten Schilddrüsentätigkeit zugehörten. Untersuchungen des Jodstoffwechsels zeigten eine normale Schilddrüsenfunktion. Es wird die Folgerung gezogen, dass atypische Fälle von angeborenem Hypothyreoidismus vollständig durchuntersucht werden sollten.

Signos de hipotireosis en encefalopatías.

Signos de retardo en el desarrollo de los centros de osificación y bajo metabolismo basal fueron encontrados en tres niños con daño encefálico cuyas edades oscilaban

entre 13 y 17 meses. La falta de aspecto mixedematoso hizo que estos signos no fueran atribuídos a anormal funcionamiento tiroideo. Los estudios del metabolismo del iodo se mostraron normales. Se aconseja estudiar completamente los casos de hipotiroidismo congénito atípico.

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From the Children's Clinic, Helsinki, Finland

Effect of Ascorbic Acid upon the Hemolysis of Human Blood Caused by Oxygen

Preliminary Report II

by NIELS RÄIHÄ

In the first report (Räihä, 1955) it was shown that the hemolysis of human blood in some cases was directly proportional to the oxygen tension (in vitro) to which the blood was exposed, and that this effect could clearly be prevented by an oral intake of Vitamin E 24 hours before the collection of the blood samples. Blood drawn from the umbilical cord generally had a much higher degree of hemolysis at atmospheric oxygen tension, but by an increase of the oxygen tension the hemolysis was observed to be fairly constant.

In the present work, however, it becomes evident that both umbilical blood and adult blood react in the same manner to the increasing oxygen tension, the only difference being that the hemolysis of blood from the umbilical cord generally is more pronounced than that of adult blood.

It is suggested by some investigators that Vitamin C as well as Vitamin E act as antioxidants in biological oxidation-reduction reactions. This relationship between these important vitamins led to the following experiments, in which the effect of ascorbic acid upon the hemolysis of human blood caused by oxygen was studied.

Materials, Methods and Results

The oxygen treatment of the blood and the measurement of the degree of hemolysis has been essentially the same as that described in the author's Preliminary Report I. It was observed that an increase of the centrifuging time to 10 min. tended to give better duplicate values. The ascorbic acid content of the blood samples was determined according to Schaffert and Kingsley. The oral dosis of ascorbic acid was in all cases 2–3 g, given to the blood donors 24 hours before the collection of the blood samples.

The hemolysis caused by oxygen was tested before and after an intake of ascorbic acid in three normal adults. The results were the same as those

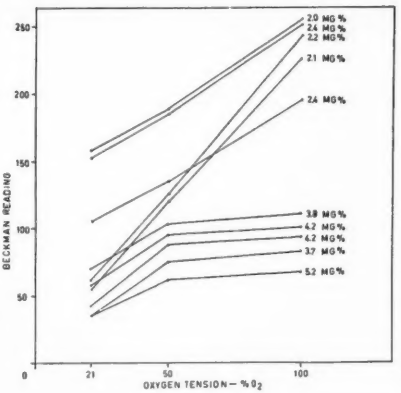

Fig. 1. Degree of hemolysis of umbilical cord blood caused by increasing the oxygen tension. The five upper curves show the degree of hemolysis when no ascorbic acid was given to the mothers before delivery. The five lower curves show the results after an oral intake of 2–3 g ascorbic acid 24 hours before delivery. The blood level of total ascorbic acid is shown at the end of each curve.

described for Vitamin E in Preliminary Report I. The increasing oxygen tension caused an increasing degree of hemolysis, which could be prevented by an oral intake of ascorbic acid. In the experiments where no previous ascorbic acid intake had occurred, the whole blood values for total ascorbic acid ranged from 1.2–1.7 mg%. In the cases where ascorbic acid had been administered the values ranged from 2.3–2.6 mg%.

Ten experiments were performed with umbilical cord blood. In five cases ascorbic acid had been administered to the mothers the day before delivery. In the other five cases no ascorbic acid was given. The results are seen in Fig. 1, with the corresponding ascorbic acid concentrations of the blood samples at the end of each curve. The umbilical blood showed a marked degree of hemolysis already at atmospheric oxygen tension, and with increasing oxygen tension the hemolysis increased to well above the corresponding values for adult blood. The increased ascorbic acid concentration of the umbilical blood inhibited the degree of hemolysis in all cases.

Discussion

It is a well-known fact that the ascorbic acid content of cord blood at birth is well above that of maternal blood (Wahren and Rundqvist, Manahan and Eastman). A decrease in ascorbic acid occurs immediately after birth (Mindlin). Later the level of ascorbic acid in the infant blood can be correlated with the intake in nutrition.

From the present work it becomes evident that a high ascorbic acid concentration of the blood has an inhibitory effect upon the hemolysis caused by increasing oxygen tension (in vitro).

After birth the oxygen tension of the blood of the newborn increases

rapidly (Smith and Kaplan), and during the first days of life there is a varying degree of bilirubinemia due to an increased breakdown of erythrocytes. If the degree of icterus neonatorum could be shown to be correlated to the level of Vitamin E and Vitamin C in infant blood, it would seem highly probable that the results in the present (in vitro) experiments hold also in vivo. Investigations along these lines are in progress.

Summary

1. Adult and cord blood was hemolysed by incubation in increasing oxygen tensions.

2. The degree of hemolysis in cord blood was generally more marked than that of adult blood.

3. Increased levels of ascorbic acid in blood had an inhibitory effect upon the hemolysis caused by oxygen.

Effet de l'acide ascorbique sur l'hémolyse du sang humain causée par l'oxygène.

Du sang de personnes adultes ainsi que du sang prélevé au cordon ombilical, ont été hémolysés par la mise en présence de tensions croissantes en oxygène. Le degré d'hémolyse du sang du cordon a été, en général, plus élevé que celui du sang des adultes. Des concentrations croissantes en acide ascorbique dans le sang ont un effet inhibiteur contre l'hémolyse causée par l'oxygène.

Die Wirkung von Ascorbinsäure auf durch Sauerstoff hämolysiertes menschliches Blut.

Erwachsenen- und Nabelschnurblut wurde durch Einwirkung von Sauerstoff in ansteigender Spannung hämolysiert. Der Grad der Hämolyse pflegte im Nadelschnurblut im allgemeinen merklicher zu sein als der des Erwachsenenblutes. Erhöhte Ascorbinsäurespiegel im Blut hatte eine inhibitorischen Effekt auf durch Sauerstoff bewirkte Hämolyse.

Efecto del ácido ascórbico sobre la hemólisis provocada por oxígeno.

Se hemolizó sangre de adultos y del cordón umbilical de recién nacidos sometiéndola a tensiones crecientes de O_2. El grado de hemólisis fúe mayor en esta última. Niveles altos de ascorbinemia mostraron efectos inhibitorios sobre la hemólisis provocada por oxígeno.

Acknowledgement

I wish to thank Mrs. K. Laine for skilful assistance.

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Appearance in Children's Sera of Substances Capable of Neutralizing Canine Distemper Virus[1]

Preliminary Report

by GUN CARLSTRÖM

Now and again it has been discussed whether the viral agent which causes canine distemper in dogs (Carré 1905) gives rise to human infections (Bryan 1928, Nicolle 1931, Whitney 1943). Most of the observations in this subject which are based on clinical or experimental evidence, are inconclusive. Recent elaboration of a serologic canine distemper test has now made available a valuable tool for immunologic investigations of this problem.

The adaptation of canine distemper virus (CDV) to developing hen's eggs (Haig 1948 and 1949, Cabasso and Cox 1949) has made it possible to use the embryonated egg as a test animal in a virus–serum neutralizing procedure. Several investigators have employed this technic to determine the presence of distemper neutralizing activity in serum (Cabasso *et al.* 1949, 1951 and 1952, Morse *et al.*, Imagava *et al.* 1953 and 1954, Baker *et al.*).

Adams, in 1953, published clinical, epidemiologic, pathologic and serologic evidence indicating a possible immunologic relationship between canine distemper and a respiratory disease in children. Acute and convalescent serum samples from patients were tested in ovo against a chick embryo-adapted CDV strain. There was no evidence of neutralization with acute serum, but convalescent serum inhibited the growth on the chorioallantoic membrane (CAM). CDV neutralization tests in chick embryos were also performed with serum samples from adults and infants. They demonstrated the lack of neutralization by infant serum and the property of neutralization by adult serum. CDV neutralizing activity was also found in human gamma globulin. Further studies in this subject were reported by Imagawa *et al.*

[1] This study was aided by a grant from the Medical Research Fund of Karolinska Institutet.

in 1953 and 1954. The results indicated that CDV neutralizing capacity could be acquired by human beings. The problem needed further exploration.

To confirm previous observations, some preliminary investigations were performed by the present author in 1953. The Lederle strain of egg-adapted CDV was inoculated on to the CAM of 8-day-old chick embryos and was found to cause lesions in the membranes clearly demonstrable on the 5th day after inoculation. Human sera were tested for neutralizing activity against egg-adapted CDV. Serum samples were collected from 4 adults, previously exposed to dogs suffering from canine distemper, and from 4 children of different ages. Sera were heated for 30 minutes at 56°C and mixed with equal volumes of virus suspension. Penicillin and streptomycin, 1000 units and 500 μg per ml, respectively, were added, and the virus–serum mixtures were held at 37°C for 2 hours and inoculated on to the CAM of 8 day-old chick embryos. Virus suspension diluted in an equal volume of broth and similarly handled served as control. It was found that all adult sera as well as sera from 2 older children, 10 and 13 years of age, inhibited virus activity. There was no evidence of neutralizing activity in sera collected from 2 small children, 4 months and $2^1/_2$ years of age. The results were in agreement with previously reported findings.

Morse *et al.*, in 1953, reported the successful propagation of an egg-adapted CDV strain intracerebrally through 18 serial passages in suckling mice. Attempts to evaluate CDV neutralizing activity in different sera by intracerebral inoculation of serum–virus mixtures, however, had yielded equivocal results.

It is the purpose of this paper (1) to report the adaptation to suckling mice of an avianized strain of CDV and the subsequent development of a neutralization test in mice, and (2) to present observations regarding CDV neutralizing activity in children's sera.

Materials and Methods

Virus.—Avianized modified canine distemper virus, Lederle strain, carried through several egg passages in this laboratory,[1] was employed. A 40 per cent suspension of infected CAM, ground and centrifuged for 10 minutes at 2500 r.p.m., furnished the supernatant fluid used as inoculum of the initial passage.

Preparation of virus.—Albino mice 24 to 48 hours old, bred in this laboratory in groups of 6 to 1 mother, were inoculated intracerebrally in the right hemisphere with 0.01 ml quantities of inoculum. All inocula contained penicillin and streptomycin, 1000 units and 500 μg per ml, respectively. The mice were sacrificed after development of typical symptoms. The length of time from appearance of symptoms until harvest did not appreciably influence the infectivity of the mouse brains. Dead mice

[1] Obtained through the courtesy of Dr. G. Rockborn, Department of Virus Research, Karolinska Institutet, Stockholm.

were discarded and never included in the harvest. The mice were killed with ether, the brains were collected and stored frozen in stoppered tubes at −60°C. The time of storage seldom exceeded 1 week. (The activity of stock virus, however, remained uniform for at least $2^1/_2$ months.) Before use, test tubes were thawed and 2 to 4 brains were pooled, ground and centrifuged for 10 minutes at 2500 r.p.m. A 10 per cent suspension of infected mouse brains in broth was used as the source of virus.

Sera.—Immune sera were collected from

1) Twelve albino mice, immunized 3 times at 4 weeks' intervals by intraperitoneal inoculation of 0.03 ml of 40 per cent suspension of avianized CDV. The mice were bled 3 weeks after the last inoculation, the sera were pooled and stored frozen at −20°C.

2) Ten albino mice, immunized twice at 2 weeks' intervals by intraperitoneal inoculation of 0.03 ml of 10 per cent suspension of mouse-adapted CDV. The mice were bled 4 weeks after the last inoculation, the sera were pooled and stored frozen at −20°C.

3) One dog immunized 3 times at 3 weeks' intervals by subcutaneous inoculation of 2 ml ferret-adapted CDV (commercial). The dog was bled 3 weeks after the last inoculation and a large quantity of serum stored frozen at −20°C. (Hyperimmune-serum pool.)

Human sera were obtained (1) from normal individuals and from patients selected at random in different wards of the Pediatric Clinic, and (2) as paired acute and convalescent sera from patients treated for various infectious diseases. Acute sera were collected within 4 days after the onset of disease and convalescent sera $1^1/_2$ to 4 weeks after the onset. The sera were separated within 24 hours after bleeding and stored frozen at −20°C. Occasionally samples were kept at 2°C for 2 to 3 days prior to separation and storage.

Neutralization technic.—A virus quantity corresponding to 0.005 ml of a 10 per cent suspension of mouse-adapted CDV was employed in all neutralization tests. This amount was just sufficient to cause uniformly 100 per cent mortality in the test mice. Virus was mixed with an equal volume of serum. Positive and negative controls were included in each test. For the positive control an immune serum was used in a constant dilution, previously ascertained to neutralize 0.005 ml of a 10 per cent virus suspension. CDV mixed with equal an amount of broth served as the negative control. Penicillin and streptomycin, 1000 units and 500 μg per ml, respectively, were added to all mixtures, and these were in the initial studies kept at 37°C for 1 hour. As this had a slightly deleterious effect on the virus, keeping at room temperature for 30 minutes was later preferred. The mixtures were inoculated intracerebrally into 24- to 48-hour-old mice. The test mice were observed daily for 2 to 3 weeks following inoculation. Animals which died within 2 days of inoculation, and mice which died later or disappeared (cannibalism) without having previously shown typical symptoms, were not included in the tabulations.

All dog and mouse sera as well as human sera used in the initial tests were heated to 56°C for 30 minutes before use. As inactivation seemed to have no noticeable influence on the results, human sera employed later in the study were tested without previous inactivation. In all serum dilutions broth served as diluent. Human sera were used undiluted. Acute and convalescent sera from the same patient were tested simultaneously.

Calculations.—The Reed-Muench method was employed to calculate 50 per cent end points (Reed-Muench).

Results

Mouse passages and neutralization tests

Avianized CDV was carried through serial intracerebral passages in suckling mice and is now in its 74th passage. The observations of the passages are summarized in Table 1. In the first passage the main part of mice

TABLE 1

Intracerebral passage of avianized CDV in suckling mice.

Passage No.	No. of mice affected/ No. inoculated*	Time in days after inoculation until appearance of nervous signs
1	35 (11)/59	6–17
2	3 (1)/12	7–11
5	2 (7)/15	6–8
8	12 (4)/16	4–9
12	11/11	5
22	8 (1)/9	3–7
36	9 (1)/10	3–5
50	11 (1)/12	4–7
74	11/11	3–7

* Numerator indicates number of mice which died or were sacrificed with pronounced spastic paralysis. The number in paranthesis indicates number of mice with observed slight nervous signs.

developed evident symptoms with clonic spasms. Several mice showed less prominent motor disturbances such as hyperkinesis, ataxia, disequilibrium and muscular twitching. Nervous signs appeared within 6 to 17 days after inoculation. In the 5 following passages, reactions were less pronounced. Some single mice developed clonic spasms and some mice showed slight nervous signs but the main part of the animals was not affected. Incubation time decreased somewhat. From the 7th passage on, there was a marked change. Within 4 to 9 days of inoculation 12 out of 16 mice developed severe spastic paralysis and died or were sacrificed. Death occurred within 9 to 11 days after inoculation. There was no great change in the following passages but a slight tendency to a gradual decrease of incubation time and intensified nervous symptoms in the mice were noted. With the 22nd passage nervous signs appeared within 3 to 7 days after inoculation, most frequently on the 5th or 6th day, and 8 out of 9 mice developed spastic paralysis and died or were sacrificed. Death occurred within 6 to 9 days after inoculation. The results were similar with all later passages. The in-

TABLE 2

Virus titer of infected brain material with different passages.

Passage No.	Virus dilutions				Titer: Neg. Log. of LD_{50}
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	
12	11/12*	5/12	2/12	0/12	1.9
18	4/6	2/4	0/6	0/6†	1.9
(33	11/11	6/12	—	—	2)
55	8/8	8/12	2/12	0/12	2.2
74	11/11	4/8	1/9	0/9	2.1

* Denominator indicates number of mice inoculated, and numerator mice which died o were sacrificed with pronounce l spastic paralysis.

† In 18th passage virus dilutions were $10^{-1.3}$, $10^{-2.3}$, $10^{-3.3}$ and $10^{-4.3}$.

fectivity of the brain material increased slowly during the earlier passages and then remained grossly unchanged, as demonstrated in Table 2.

By employment of the neutralization technic outlined above the mouse-adapted agent was tested against different sera. Serum from a dog immunized with ferret-adapted CDV, serum from mice immunized with egg-adapted CDV, homologous immune serum obtained from mice immunized with infected mouse brains and serum from normal mice were employed. All sera were inactivated and used undiluted. One hundredth ml of a mixture of equal volumes of 10 per cent mouse brain suspension and serum was injected intracerebrally in 24- to 48-hour-old mice and the test animals were observed for 3 weeks. All immune sera prevented symptoms in the test mice but normal mouse serum did not show neutralizing activity (Table 3). Human sera were also employed; they demonstrated the property of neutralization by adult serum and the lack of neutralization by serum from a $2^1/_2$-year-old boy. The human sera employed were, in the preliminary

TABLE 3

Neutralization tests in mice employing infected brain material and various samples of undiluted sera.

Serum from normal mice	Mice immunized with avianized CDV	Mice immunized with infected mice brains	Dog immunized with ferret-adapted CDV	Man (adult)	Child ($2^1/_2$ years old)
8/12	0/17*	0/11	0/5	0/12	5/8

* Denominator indicates number of mice inoculated, and numerator mice which died o were sacrificed with pronounced spastic paralysis.

investigation, tested in chick embryos against egg-adapted CDV with corresponding results. No additional investigations were made to confirm the identity of the mouse-adapted agent. Cross neutralization tests were not performed.

Table 4 shows the result from a quantitative neutralization test using mouse-adapted CDV and a 10-fold serial dilution of dog immune serum. The neutralizing titer of serum, expressed as neg. Log. of 50 per cent neutralizing dose dilution, was found to be 3.3.

TABLE 4

Quantitative neutralization test employing the serum dilution method with mouse-adapted CDV and 10-fold dilutions of immune dog serum.

Serum dilutions				Negative Log. of ND_{50}
10^{-2}	10^{-3}	10^{-4}	10^{-5}	
0/12*	5/12	11/12	11/12	3.3

* Denominator indicates number of mice inoculated, and numerator number of mice which died with spastic nervous symptoms.

Neutralizing substances in human sera

To evaluate the general distribution of CDV neutralizing activity in a human population in Stockholm, serum samples from adults and from children of different ages were collected and examined in 1954 and 1955. Normal individuals and patients in the Pediatric Clinic, Karolinska Sjukhuset, treated for various diseases (mainly acute infections) were employed in this study. The findings are summarized in Figure 1. CDV neutralizing capacity was seldom found in children less than 4 years old. Between the ages of 4 years and 6 years, some individuals showed the property of neutralization, some did not. Most children between 6 and 10 years demonstrated neutralizing activity, and so did all individuals more than 10 years of age.

While this manuscript was in preparation, Karzon, in 1955, published studies of antibodies against canine distemper virus in man. He presented the pattern of immune response against CDV found in adults and children of different ages in New York State, U.S.A. Newborn infants were regularly found to possess antibody which was lost by the age of 6 months. Very few children between 6 months and 24 months showed antibody. Beginning at 2 years of age, the number of children with antibody rose rapidly approaching an incidence of 100 per cent by 10 years of age. Of 59 adults

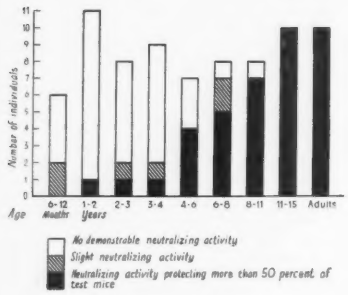

Fig. 1. Distribution of neutralizing activity i adults and children of different ages.

all possessed antibody. His findings correspond to the observations pre sented in this report. A different laboratory technic and the limited numbe of investigated individuals in the present study may account for a sligh tendency to a later appearance of neutralizing substances in the Swedish population. It has to be considered, however, that there may be a rea epidemiological difference.

Attempts have been made to find a relationship between illness in man and the acquirement of neutralizing activity in human sera. Acute and convalescent sera taken from children treated in Karolinska Sjukhuset in 1954 and 1955 for various infectious diseases were tested for CDV neutralizing activity. Diseases subject to the investigations have been respiratory infections, exanthematous diseases, central nervous system infections and gastroenteritis. The capacity of CDV neutralization was not acquired during the illness in any of the investigated cases.

Two patients, 3 and 4 years old, received human gamma globulin, 0.3 ml/kg, given prophylactically after exposure to measles. In both cases a subsequent increase of CDV neutralizing capacity was found. Sera collected 3 and 4 days before treatment did not show neutralizing capacity, but serum samples obtained 7 and 10 days after administration of gamma globulin protected more than 50 per cent of test mice from death. The CDV neutralizing activity of human gamma globulin has previously been subjected to study by several investigators (Adams, Imagawa *et al.*, Karzon).

Discussion

Karzon has presented evidence indicating the true antibody nature of CDV neutralizing substances found in human sera. This supports the assumption that CDV neutralizing activity is acquired by man as a result of infection. According to the distribution of neutralizing substances in humans, canine distemper virus or an antigenically related infectious agent

seems to be ubiquitous and well adjusted to man. The question whether infection with this agent may also give rise to clinical symptoms in human beings is still unanswered. Canine distemper virus has never been isolated from man, and Adams' observations with clinical and serologic evidence indicating a relationship between canine distemper virus and human illness so far have not been confirmed.

Studies are continuing in healthy children and in patients with infectious diseases. Mainly children less than 6 years of age are being studied, who, according to the pattern of human immune status, would represent the age groups most likely to respond to infection with clinical manifestations.

Summary

An avianized strain of canine distemper virus has been adapted to suckling mice, and a reproducible test for the measurement of neutralizing substances against CDV was elaborated.

The distribution of CDV neutralizing activity in man has been studied. In adults and most children more than 6 years of age, CDV neutralizing capacity has been found, but seldom in children less than 4 years old. Between the ages of 4 and 6 years some individuals demonstrated the capacity of neutralization and some did not. Paired acute and convalescent sera from children with various infectious diseases were investigated. So far attempts to find a relationship between a human illness and the development of CDV neutralizing activity in children's sera have yielded negative results.

La démonstration dans le sérum des enfants de substances capables de neutraliser le virus de la maladie des jeunes chiens (MJCh). Communication préliminaire.

Une colonie de MJCh cultivée dans l'embryon de poulet a été adaptée aux rats lactants et une test reproducible pour mésurer les substances neutralisantes de MJCh a été élaborée. La distribution humaine de l'activité MJCh neutralisantes a été étudiée. Les adultes et la plupart des enfants agés de plus de 6 ans ont une capacité MjCh neutralisante, capacité rarement trouvée chez les enfants de moins de 4 ans. Entre 4 et 6 ans seulement quelques enfants montrent une capacité neutralisante. Le sérum des enfants aiguës et des convalescents des différents maladies infectieuses a aussi été investigué. Des essaies faites pour trouver une relation entre maladie humaine et développement d'activité MJCh neutralisante ont donné des résultats négatives.

Das Auftreten von Substanzen in kindlichen Seren, die in der Lage sind, das Hunde-Staupe-Virus (HSV) zu neutralisieren. Vorläufiger Bericht.

Ein in Hühnerembryonen gezüchteter Stamm von Hunde-Staupe-Virus ist an laktierende Mäuse adaptiert worden und ein reproduzierbarer Test für die Messung neutralisierender Substanzen gegen HSV wurde ausgearbeitet. Die Verteilung von HSV-neutralisierender Aktivität beim Menschen ist einer Untersuchung unterzogen worden. Bei Erwachsenen und den meisten über 6 Jahre alten Kindern ist HSV-Neutralisationsaktivität gefunden worden, jedoch selten bei Kindern unter 4 Jahren. Zwischen dem Alter von 4 und 6 Jahren zeigten einige Individuen die Fähigkeit der

Neutralisation und einige nicht. Gepaarte akute und konvaleszente Seren von Kinde[r] mit verschiedenen Infektionskrankheiten wurden untersucht. Versuche, eine Bezi[e]hung zwischen einer menschlichen Erkrankung und der Entwicklung von HSV-neutralisierender Aktivität in kindlichen Seren zu finden, haben bisher negati[ve] Resultate ergeben.

Demostración en le suero de niños de sustancias capaces de neutralizar el virus de m[o]quillo de perro (VMP). Comunicación preliminar.

Una cepa, cultivada en embrión de pollo, del virus de moquillo de perro fué ada[p]tada a ratas lactantes y un test reproducible para medir sustancias neutralizantes d[el] VMP fué elaborado. Se estudió la distribución en el hombre de la actividad VMP neutralizante. En la mayoría de los niños de mas de 6 años y en los adultos fué encon[-]trada capacidad VMP neutralizante, capacidad raramente demostrada en niños m[e]nores de 4 años. Entre las edades de 4 y 6 años algunos niños demuestran capacidad neutralizante mientras otros no lo hacen. Suero de niños agudos y convalecientes d[e] varias enfermedades infecciosas fué también investigado. Los intentos hechos para demostrar una relación entre enfermedad humana y desarrollo de actividad VMP neutralizante en niños han dado resultados negativos.

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PROGRESS IN PEDIATRICS

Systemic Lupus Erythematosus in Childhood

A Clinical Study

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The discovery of the occurrence of the LE-cell phenomenon in systemic lupus erythematosus by Hargraves, Richmond & Morton (1948) has improved the possibilities for diagnosis of this disorder. As a consequense, it has also been possible to perform more reliable clinical studies. During recent years the enormous variability of symptomatology and clinical course has been reported in a great number of publications. Extensive surveys were published by Gold & Gowing (1953) and by Harvey, Shulman, Tumulty, Conley & Schoenrich (1954).

It is a well-known fact that systemic lupus erythematosus may appear in childhood. In some earlier studies a few children have been included. Sporadic case reports have also appeared in the pediatric literature (Pehrson and Fornara & Genesi), but no real studies of the clinical features of systemic lupus erythematosus in childhood have been reported. The purpose of this communication is to describe, on the basis of the investigation of 11 patients, the symptoms of systemic lupus erythematosus and the course of the disease when it occurs in childhood. Possible differences of the course in adults and children will be discussed.

General Survey of the Material

During the period September 1952 to September 1955, 11 patients with systemic lupus erythematosus have been observed in the Pediatric Clinic, Karolinska Sjukhuset. Such factors as the demonstration of LE-cells, the appearance of a butterfly rash, typical pathological findings and the clinical course were considered as evidence of the diagnosis.

A short survey of the patients studied is given in Table 1. There were 6 female and 5 male children. The youngest patient was 5 years of age when the disease started. Beside such vague symptoms and signs as fatigue, anorexia, fever and high sedimentation rate, joint pain was the first symptom

in most patients, but other initial features included discoid lupus, ulcerative colitis, false positive serologic reactions and nephropathy. Six patients have expired from their disease. It was not possible to classify the cases into acute, subacute or chronic types because of the variability in the symptomatology during the course of the disease. Cases starting as an acute illness became subacute, or in a more chronic progressing disease acute relapse occurred. However, roughly speaking, most cases could be considered subacute. In none of the patients did the family history reveal any special information.

Disorders and Abnormalities Before the Start of the Disease

One of the patients suffered from an allergic eczema when 2 years old; the eczema completely disappeared within a few years. Otherwise there was no history of allergic disease in any patient. One of the patients (Case 3) had congenital heart disease (? anomalous venous return). In another patient (Case 6) there had been symptoms of diabetes since the age of 3 years. The rest of the patients were said to have been quite healthy earlier.

Possible Inducing Factors

Ever since Osler's description of systemic lupus erythematosus it has been generally accepted that ultraviolet light might activate cutanous and probably also visceral manifestations of systemic lupus erythematosus. However, it has never been proved that the exposure to sunlight induces the disease. In our material the first symptoms were spread out over the whole year, thus there was no connection between the onset of the disease and the incidence of exposure to ultraviolet light. In two patients a relapse was observed after exposure to sunlight.

Focal infections as the cause of systemic lupus erythematosus have been repeatedly discussed. Shearn & Pirofsky were able to find evidence of focal infection in 50 per cent of their patients. From our material, it was impossible to find any evidence for the hypothesis that focal infections might be connected with the etiology of systemic lupus erythematosus.

Signs and Symptoms

A general survey of the incidence of symptoms from various organs is given in Fig. 1.

Cutaneous symptoms.—Polymorphic cutaneous manifestations were observed in all patients investigated. Erythema localized around the nail folds and on the finger tips, macular erythema and small spindel-shaped telangiectasis of varying localization were occasionally found. Almost regularly

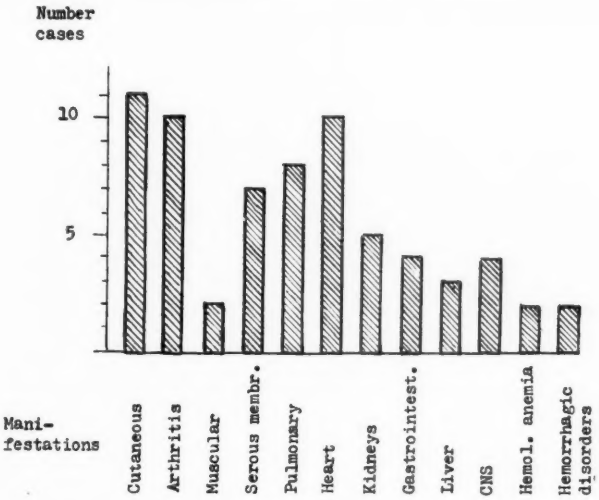

Fig. 1. Chart showing the incidence of symptoms from various organs during the course of the disease in 11 patients with systemic lupus erythematosus.

there also were small dermal pink or slightly cyanotic infiltrations, occasionally with necrosis, but transient in nature. They usually were found around the elbows, wrists, kneejoints and ankles. Pink striation was often observed.

Typical butterfly rash lasting for a period of a few weeks up to several months was seen in 5 of the patients. In one, a butterfly rash appeared repeatedly in association with acute relapses. In another (Case 8), there was a marked wide-spread depigmentation with areas of intense pigmentation, while two others showed typical vitiligo. Erythema nodosum lasting for 3 weeks was found in one patient.

In a girl aged 8 years (Case 10), the disorder started as a discoid lupus erythematosus with a typical lesion localized to the left cheek. At the onset, there were no other symptoms. Within a few weeks there was rapid progress of the local cutaneous lesion with the development of edema, deep infiltrations and skin necrosis (Fig. 2). After another week the girl also developed symptoms of a systemic disease with high fever, arthritis and moderate hepatomegaly. The course of the illness in this patient seems to be strong evidence for the hypothesis that discoid and systemic lupus erythematosus are the same pathological entity (cf. Montgomery & McCreight; Cohen & Cadman).

Joint symptoms.—As is shown in Table 1 arthritis was the initial symptom in 7 out of 11 patients investigated. During the course of the disease arthritis

Fig. 2. A photograph on admission of a child (Case 10) with discoid lupus erythematosus as the first symptom of the systemic disease. Hydrocortisone treatment caused a rapid improvement of the skin lesion.

also was a prominent part of the clinical manifestations in 10 of the children. The joint symptoms usually were acute. In some patients they were localized to the finger joints and associated with synovitis, in others they were mainly localized to the large joints and migrated. Most often they subsided rapidly, but acute recurrences took place in association with relapses of the

TABLE 1

Data of the patients investigated.

Cases	Sex	Age by onset years	Initial symtom	Duration	Present state
1. R.	Female	13	Arthritis	9 months	Dead
2. G.	Female	7	Arthritis	7 years	Dead
3. H.	Female	12	Ulcerative colitis	9 months	Improved
4. L.	Female	11	Arthritis	18 months	Dead
5. M.	Female	11	Arthritis. False positive serologic reactions	5 years	Progressive
6. S.	Male	7	Arthritis	1 year	Unchanged
7. F.	Male	5	Arthritis	18 months	Remission
8. Ru.	Male	11	Arthritis	2 1/2 years	Dead
9. T.	Male	8	Ulcerative colitis	4 years	Unchanged
10. W.	Female	8	Discoid lupus	6 months	Dead
11. E.	Male	11	Nephropathy	21 months	Dead

general disorder. In one patient permanent joint deformities like those found in rheumatoid arthritis developed.

Muscular symptoms.—Slight swelling and tenderness of the muscles in the legs were observed in two of the patients in association with symptoms of acute arthritis. In one of the children (Case 11) intense abdominal pains which could be attributed to tenderness of the muscles in the abdominal wall were seen during the initial acute stage.

Mucous membranes.—Redness and dryness of the mucous membrane of the oral cavity was noted in about 50 per cent of the patients. In three cases there were repeated aphtous ulcers.

Serous membranes.—Seven patients had symptoms due to involvement of the serous membranes. Six had pericardial effusion, 6 pleurisy and 3 ascites. In three of the patients with hydrothorax a nephrotic syndrome with low serum albumin level was also present. Thus, in these patients, the accumulation of fluid might also have been caused by changes of the colloid osmotic pressure of the plasma. In the other patients the symptoms of pericarditis or pleurisy appeared in the early course of the disease and disappeared completely when the patients went into remissions.

Symptoms of cardiac involvement.—Cardiac disease was recognized during life in 10 cases. In the early course of the disease, there were rather nonspecific signs such as the appearance of systolic murmurs. During progress of the disease more definite symptoms of heart disease appeared such as

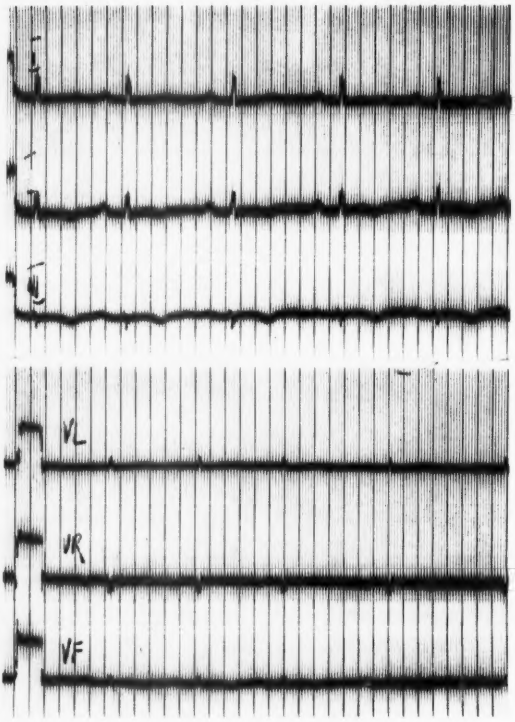

Fig. 3. Electrocardiogram from a patient (Case 5) who developed acute heart failure during the course of systemic lupus erythematosus. Note the isoelectric and negative T waves.

enlargement of the heart and abnormalities in the electrocardiogram. In one patient (Case 5) arrhythmia appeared in connection with congestive failure. Fig. 3 shows the electrocardiogram of this patient. In one of the patients a combined aortic valvular disease developed (Case 9).

As is obvious, the heart symptoms were quite variable which is in accordance with the view that different pathological types of cardiac damage may occur (cf. Liebow & Feil).

Pulmonary involvement.—On repeated roentgenological examinations pulmonary infiltrations were observed in 8 of the patients. In most cases transient bilateral infiltrations were localized in the lower lobe. The changes usually resembled those described by Thorell. However, bigger infiltrations in only one of the lungs were also observed. In one patient (Case 9) there was an infiltration in the left lower lobe combined with an increase of the

paratracheal shadow giving the same appearance as in pulmonary primary complex.

One of the patients had symptoms suggesting a primary pulmonary hypertension of the type of Ayerza's disease. It was a 12 years old girl (Case 2) with an intense cyanosis and clubbing of the fingers. Her total capacity as well as her vital capacity was slightly diminished. The arterial oxygen saturation was raised to 87 per cent after the inhalation of 100 per cent oxygen. The cyanosis could not be explained by a heart disease.

Symptoms of renal disease.—In 2 cases out of 5 the death was primarily referable to renal involvement. In another case (Case 8) which terminated fatally symptoms of severe renal disease developed with gradually increasing amounts of protein in the urine, gross edema, hypertension and uremia. In this patient, however, there was also severe cardiac involvement and symptoms of extensive damage to the central nervous system. In all three patients with severe renal disease a marked glomerular insufficiency was associated with a nephrotic syndrome, hypertension, and the development of hyposteneuria. No evidence of a disturbance in the acid-base regulating mechanism was noted.

In two other patients there were slight hematuria and proteinuria but without any obvious impairment of the filtration.

Gastrointestinal symptoms.—In numerous publications gastrointestinal involvement has been reported in systemic lupus erythematosus. The commonest symptom is diarrhea, but more serious changes such as necrosis of large areas of the gut wall (Garfield, Steale & Houghton) may be seen.

Four of our patients complained of gastrointestinal symptoms. Two had periods of diarrhea, and in the other two the symptoms resembled those seen in chronic ulcerative colitis. In one of this children (Case 3) the clinical picture initially resembled typhoid fever, but after two months the features were those of an ulcerative colitis with typical findings both on proctoscopy and X-ray investigation of the colon.

Liver involvement.—Hepatomegaly was noticed in 6 of the patients but as revealed from the bromsulphtalein excretion test and the presence of jaundice there was serious liver damage only in three of these patients (bilirubin levels 1.4–5.3 mg per 100 ml). In two patients (Cases 2 and 4) the clinical picture was typical of liver cirrhosis in the final stage; both of them probably died from liver coma.

Spleen.—Splenomegaly was noticed in four patients.

Glandular enlargement.—A slight generalized lymphadenopathy was seen in only two of the patients. This low incidence of glandular involvement is not in accordance with the statement of Dubois who has claimed that lymphadenopathy is most likely to occur in young patients.

Central nervous system involvement.—Lesions of the central nervous system are reported to occur frequently in systemic lupus erythematosus (Lewis, Sinton & Knott; Sickert & Clark). The symptomatology can be very variable. Generalized and focal convulsions, paresis, vertigo, nystagmus, cortical blindness, and disorders of movement, as well as psychiatric abnormalities may be seen as evidence of neurologic involvement.

In our material five of the patients had definite symptoms referable to the central nervous sytem. Two showed apathy, mental depression, and paranoid reactions and the remaining three convulsions. Serious damage to the central nervous system was noted in Case 8. The neurologic symptoms started with longstanding epileptic seizures one year efter the onset of the disease, followed by severe psychic changes with a progressing mental disturbance in association with hallucinations. In the final stage the patient developed a homonymous hemianopsia. Electroencephalographic studies revealed highly pathological registrations with slow voltage and low amplitude. One of the patients expired in *status epilepticus.*

Ocular manifestations.—The occurrence of blurred discs, central exudate, and venous congestion has been reported in systemic lupus erythematosus (Clifton & Greer). Three of our patients exhibited retinal changes. Blurred discs were observed in all these cases, in one there was marked papilledema with a protrusion of 2 dioptries which was transient in nature. In the terminal stage exudate and hemorrhages in the central part of the retina were found in one of the patients.

Anemia.—In the early course of the disease anemia was no predominant symptom in the patients investigated, but in the more advanced stage of the disease anemia was severe in four of the patients.

Hemorrhagic disorders.—Petechia were frequently observed in the children with systemic lupus erythematosus. One of the patients bled from the nose, the intestines and the kidneys.

Laboratory Findings

LE-cell phenomenon.—This was demonstrated in only 5 out of the 11 cases in our series. It is difficult to interpret the low incidence of a positive test since Haserick was able to demonstrate the phenomenon in 23 out of 25 patients with systemic lupus erythematosus. One explanation might be that cortisone or ACTH treatment in several cases was started before there were any attempts to demonstrate these cells. In those cases with a positive test the LE-cells regularly were found before hormone therapy was instituted. During treatment the phenomenon disappeared. In one patient repeated attempts to demonstrate LE-cells failed despite absence of hormone therapy.

TABLE 2

Hematological data in 11 children with systemic lupus erythematosus.

Case	Hemoglobin g per 100 ml	RBC mill. per c.mm	Reticulocytes per cent	WBC per c.mm	Eosinophils per cent	Lymphocytes per cent	Trombocytes per c.mm × 1,000
1.	4.3– 9.2	1.1–3.7	0.4– 8.8	1,900– 5,900	0–7	10–37	140–233
2.	10.1–12.4	3.7–4.3	0.4– 1.5	1,900– 4,500	0–3.5	36–57	265
3.	11.2–13.6	3.7–4.2	3.3	8,800–16,000	1.5–5	13–30	386–486
4.	7.0–10.3	2.4–4.0	0.4– 4.0	2,400– 6,000	0	34–45	135–200
5.	7.7–11.5	2.9–3.6	0.4– 4.0	2,100– 5,200	0.5–5	32–58	198–290
6.	11.2–12.2	3.9–4.6		3,600– 4,000	6–8	17–39	105
7.	8.5–12.2	2.4–4.2	0.9– 4.3	4,500– 9,600	0–8	7–47	189–296
8.	6.4–10.0	2.6–4.3	0.9– 2.1	2,000– 9,700	3–7	17–42	24–382
9.	7.5–11.3	3.1–4.1	0.8– 2.5	6,800–19,000	0–8.5	13–27	194
10.	9.8–12.1	2.5–3.8	0.6– 5.6	3,800– 9,400	0–1	21–35	146–234
11.	3.4–12.7	1.4–3.1	1.2–11.0	1,900– 5,200	1–13	6–41	55–258

In this case typical lesions of systemic lupus erythematosus were seen at necropsy.

Hematologic findings.—As is shown in Table 2, anemia was present in 8 of the patients. In three patients who had a severe anemia there was a high reticulocyte count indicating the presence of a hemolytic syndrome as the main cause of anemia, since no source of blood loss could be found. The direct Coombs' test was negative in all these cases and no irregular agglutinins could be demonstrated. The high incidence of moderate anemia is in agreement with the findings in earlier investigations. Anemia has been found in practically all patients with systemic lupus erythematosus at some time during their illness. (Michael, Vural, Bassen & Schaefer). In cases with severe anemia a hemolytic syndrome may be the presenting symptom of the systemic disease (Dubois; Meacham & Weisberger).

Six of our patients had a leucopenia with a white cell count below 6,000 per c.mm (Table 2). In the two cases with symptoms of chronic ulcerative colitis the number of white cells was found to be up to 16,000 per c.mm during periods of severe symptoms. Earlier, MICHAEL *et al.* have found that the low white cell count in systemic lupus erythematosus is due to a lymphopenia and that there is a normal leucocyte response to acute infections. Eosinopenia was not regularly present in our material; on the contrary, eosinophilia was found in 6 instances.

Definite trombocytopenia which is reported to occur occasionally (Michael *et al.*; Eversole) was observed only twice in our series.

TABLE 3

Total serum protein concentration and the concentration of different protein fractions in 11 cases of systemic lupus erythematosus.

Case	Total protein g per 100 ml	Relative concentration in per cent					Absolute values, g per 100 ml				
		Album.	α_1-glob.	α_2-glob.	β-glob.	γ-glob.	Album.	α_1-glob.	α_2-glob.	β-glob.	γ-glob.
1.	5.8	33	10	22	13	22	1.9	0.7	1.3	0.7	1.3
2.	9.7	27.6	2.7	4.3	6.2	59.2	2.7	0.3	0.4	0.6	5.7
3.	9.5	33		16	6	45	3.0		1.5	0.6	4.4
4.	12.4	29.2	3.7	6.0	9.9	52.2	3.6	0.5	0.6	1.2	6.5
5.	8.1	45.4	5.4	7.8	7.9	33.5	3.7	0.4	0.6	0.6	2.8
6.	6.6	36	4	14	13	33	2.4	0.3	0.9	0.9	2.1
7.	7.6	45.4	6.7	13.2	10.8	23.9	3.5	0.5	1.0	0.8	1.8
8.	6.5	28	5	15	11	41	1.8	0.3	1.0	0.7	2.7
9.	6.5	43		15	16	26	2.7		1.0	1.0	1.8
10.	6.1	54.5	4.1	6.8	5.8	29.8	3.3	0.2	0.4	0.3	1.9
11.	5.9	31.0	16.0	16.3	13.5	23.2	1.7	1.0	1.0	0.8	1.4

Coagulation defects.—Studies of the hemostasis revealed a prolongation of the clotting time in two patients (Cases 5 and 11). In Case 11 the prothrombin consumption was markedly impaired but the thromboplastin generation test according to Biggs & Macfarlane was normal, a finding suggesting the presence of an anticoagulant. Earlier, FRICK, on the basis of studies on the occurrence of anticoagulants in systemic lupus erythematosus, has proposed the presence of thromboplastin inhibitors in those cases with a prolonged clotting time.

Serum proteins.—In agreement with earlier investigations (cf. Bille) there was a hyperglobulinemia in all cases, as is shown in Table 3. As revealed from paper electrophoretic separations of the serum proteins (open strip method as described by Durrum) the hyperglobulinemia was due mainly to a abnormally high γ-globulin level, the absolute concentration varying between 1.5 and 6.5 g per 100 ml. The highest γ-globulin concentration was found in the two patients (Cases 2 and 4) with liver cirrhosis, whose total serum protein levels were 9 and 12 g per 100 ml, respectively. In most cases, the albumin level was lower than under normal conditions. In the three patients who had a nephrotic syndrome albumin content of the serum was greatly reduced.

Electrophoretic separation of the urinary proteins in those patients who exhibited symptoms of a nephrotic syndrome revealed a very high urinary loss of γ-globulin, as shown in Table 4. The fact that the serum γ-globulin

TABLE 4

Electrophoretic analysis of the urinary proteins in 3 patients with systemic lupus erythematosus associated with a nephrotic syndrome.

Case	Albumin, per cent	α_1-globulin, per cent	α_2-globulin, per cent	β-globulin, per cent	γ-globulin, per cent
1	70		4	3	23
8	23	16	11	13	37
11	61		23		26

level remained markedly elevated, although there was a pronounced loss, points out the high capacity for production of this globulin fraction in systemic lupus erythematosus. However, due to the low albumin level in these patients, the total serum protein concentration was found to be below 6 g per 100 ml.

Harvey *et al.* have concluded from their studies that there exists a correlation between the γ-globulin level and the occurrence of LE-cells. We have been unable to confirm this suggestion on the basis of our material.

Serologic reactions.—As revealed from the antiglobulin test of Coombs, incomplete antibodies was demonstrated only in one patient.

False positive Wasserman and Kahn reactions persisted during the whole period of observation (5 years) in one of the children (Case 5).

In none of the patients was there a significant elevation of the antistreptolysin titer (Table 5). The antistaphylosin titer was high in several patients.

TABLE 5

Antistreptolysin titer and antistaphylolysin titer in 11 children with systemic lupus erythematosus.

Case	Antistreptolysin titer units/ml	Antistaphylolysin titer units/ml
1	360	2.5
2	2,000	1.1
3	—	—
4	—	—
5	100	0.4
6	64	14.0
7	200	1.0
8	560	0.8
9	400	2.0
10	45	0.25
11	400	11.0

TABLE 6

PAH and inulin clearance in one patient with severe kidney damage in association with systemic lupus erythematosus.

Case	Time after the onset of the disease, months	PAH clearance ml per min.	Inulin clearance ml per min.	N.P.N. mg per 100 ml
11	7	93.8	12.5	82

The significance of this finding remains obscure because there were no indications of previous staphylococcal infections.

Following active immunization against typhoid fever, those two patients who were tested showed a normal antibody response.

Studies of renal function.—In the patients with a severe nephropathy uremia developed. In one instance the renal function was studied by means of paraaminohippuric acid and inulin clearance. From the results which are shown in Table 6 it is quite clear that there was an excessive impairment both of glomerular filtration and blood flow.

Treatment and Course

Six patients have expired from their disease. The duration between the first symptoms of the disease and the fatal termination varied between 6 months and 7 years. Evidence of progressive impairment of the kidney and liver function were found to be ominous signs. Two of the deaths were due to progressive renal failure, two were principally due to liver coma and one to involvement of the central nervous system. Of the patients who still are alive, one has suffered from her disease for 5 years, in the rest the time since the onset is shorter. Such complications as severe infections have been rare. Symptoms of a septic disease with multiple big subcutaneous abscesses occurred only in one case in the terminal stage.

All patients except the two with severe nephropathy were treated with corticotropin or adrenal steroids. There had been evidence of the disease for a variable period of time before they first received therapy, the pretreatment period varying between one month and two years. When cortisone or hydrocortisone was used, the initial daily dose generally varied from 100 to 300 mg, the maintainance dose depended upon the level necessary to induce a remission and was then decreased successively. When corticotropin was used, therapy was started with 50–100 mg per day, given intramuscularly in four divided doses. Every day, 2 to 4 g of potassium chloride were routinely administered orally to prevent the possible development of hypokalemia. With this treatment a remission lasting for a varying period of

time was regularily induced. Most patients required a maintainance dose but in two cases it was possible to stop hormone treatment without the occurrence of a relapse. Both these patients have remained in a good state during a period of 12 and 6 months, respectively.

Grossly, our experience of the efficiency of hormone treatment has been the same as that reported by Soffer, Lademann & Brill. However, after the occurrence of liver damage no significant improvement of the liver function was obtained by therapy. In one patient (Case 8) with a nephrotic syndrome but without any elevation of the serum urea level, the treatment initially caused a dramatic remission, but after about 2 weeks the patient developed acute symptoms of congestive failure. A prolonged period of frequent epileptic seizures started at the same time.

Pathologic Findings

Skin biopsies from areas showing different types of cutaneous involvement were performed in 8 patients. In order to avoid non-specific reactions (cf. Goeckermann & Montgomery), only areas with changes that had lasted for more than 14 days were used. Changes consistent with a diagnosis of systemic lupus erythematosus were seen in all specimens.

Lymph node biopsies were performed in 2 patients. Only non-specific changes were observed.

Autopsy was performed in 4 patients. In 3 of the cases the investigation revealed systemic visceral lesions of the same appearance as those usually reported in systemic lupus erythematosus (cf. Libman & Sacks; Klemperer, Pollack & Baehr; Kaiser; Baggenstoss; and others). In the remaining case there was only found a diffuse non-specific encephalitis.

General Conclusions

Our material of systemic lupus erythematosus in childhood included 5 male and 6 female children. The lack of a sex difference seems remarkable since in adults the disease is known to occur predominantly in females. In the series reported by Baehr, Klemperer & Schifrin there were 22 females out of 23 patients. Earlier, Gold & Gowing have concluded that the sex difference is not as marked in young patients as in older age groups.

Gold & Gowing found acute infections previous to the onset of systemic lupus erythematosus in a great number of their patients and hypothesised that sulphonamide or penicillin as well as exposure to sunlight might have been precipitating factors. No such connection is evident in our material.

When the symptomatology and the course in our cases of systemic lupus erythematosus are compared with other large series, one gets the impression

that though the disease runs a more malignant course in childhood the initial symptoms seem to be the same. Harvey *et al.* concluded from their material that the disease starts with fever and arthritis in about 50 per cent; this is in agreement with our findings.

The same cutaneous and visceral lesions as those earlier reported in systemic lupus erythematosus have been demonstrated in our material, but we also saw lesions which have not been described previously. Two cases exhibited symptoms typical of chronic ulcerative colitis and signs suggesting the presence of a primary pulmonary hypertension were seen in another patient. The appearance of ulcerative colitis in the course of a systemic connective tissue disease has already been reported in association with necrotizing angiitis (Wasserman, Krosnick & Tumen). While jaundice has been observed in a few cases of systemic lupus erythematosus, usually in association with hemolytic anemia, liver cirrhosis has never been described, though nonspecific liver changes are frequently observed.

The relatively great number of children with systemic lupus erythematosus admitted to this clinic in recent years demonstrates that the disease is not too rare in childhood. Why so many cases have been diagnosed recently remains unknown, but an actual increase in the incidence of the disease in Sweden is possible.

Summary

The clinical findings and the results of the laboratory investigations in 11 children with systemic lupus erythematosus have been presented.

From the results of these studies it is concluded that the clinical features of systemic lupus erythematosus are similar in childhood and in more advanced age groups although the disease seems to run a more malignant course in young patients. In our material the number of males was about the same as the number of females, indicating that no sex difference in the incidence of the disease exists in childhood.

In addition to the principal lesions reported earlier in adults, chronic ulcerative colitis, liver cirrhosis and primary pulmonary hypertension were found in our material.

There was regularly a marked elevation of the serum γ-globulin level, and in the patients with liver cirrhosis the concentration of this protein fraction was extremely high. The fact that the level remained relatively high even in patients with a nephrotic syndrome with consequent high urinary loss of γ-globulin points to an intense production of this serum protein fraction in systemic lupus erythematosus.

It is concluded that systemic lupus erythematosus is not extremely rare in childhood.

Le lupus érythémateux disséminé chez l'enfant. Etude clinique.

Sont présentés dans l'article les aspects cliniques et les résultats de laboratoire dans 11 cas de lupus érythémateux disséminé chez l'enfant. De cette étude ressort que les signes cliniques du lupus érythémateux disséminé sont identiques dans l'enfance et à un age plus avancé, encore que l'affection suive une évolution plus maligne chez les malades plus jeunes. Dans le groupe étudié, le nombre de garçons et de filles était à peu prés identique, et il n'y avait donc aucune influence du sexe. Outre les lésions

habituellement décrites chez l'adulte, on notait chez les enfants de la colite ulcéreuse, de la cirrhose hépatique et de l'hypertension pulmonaire essentielle. Le taux de la gammaglobuline sérique était toujours élevé, et chez les malades atteints de cirrhose la concentration de la fraction protéïque demeurait cependant très élevée. La constatation d'un taux resté relativement haut, même chez des malades atteints d'un syndrome néphrotique (dont la conséquence est une importante déperdition urinaire de gammaglobulines) traduit la production considérable de cette fraction des protéïnes au cours du lupus érythémateux disséminé. La conclusion à tirer de cette étude est que le lupus érythémateux disséminé n'est pas une grande rareté dans l'enfance.

Lupus erythematodes disseminatus bei Kindern. Eine klinische Studie.

Die klinischen Befunde und die Resultate der Laboratoriumsuntersuchungen von 11 Kindern mit generalisiertem Lupus erythematodes werden vorgelegt. Aus den Resultaten dieser Studien wird geschlossen, dass die klinischen Merkmale des Lupus erythematodes im Kindesalter und in mehr vorgerückten Altersgruppen ähnlich sind, obgleich die Erkrankung bei jungen Patienten maligner zu verlaufen scheint. Bei den vorliegenden Gruppen von Kindern war die Anzahl der männlichen ungefähr dieselbe wie die der weiblichen Patienten, was zeigt, dass in der Kindheit kein Geschlechtsunterschied im Vorkommen dieser Erkrankung herrscht. Ausser den bei Erwachsenen bekannten Grundschäden wurden bei diesen Kindern chronische ulceröse Colitis, Lebercirrhose und primäre pulmonale Hypertension gefunden. Es war regelmässig eine deutliche Erhöhung des Serum-Gammaglobulin-Spiegels vorhanden und bei den Patienten mit Lebercirrhose war die Konzentration der Proteinfraktion extrem hoch. Die Tatsache, dass der Spiegel selbst bei Patienten mit einem nephrotischen Syndrom und folglich hohem Verlust an Gammaglobulin durch den Urin relativ hoch blieb, deutet auf eine intensive Produktion dieser Serumproteinfraktion bei Lupus erythematodes disseminatus hin. Es wird abschliessend darauf hingewiesen, dass Lupus erythematodes disseminatus im Kindesalter nicht extrem selten ist.

Lupus eritematoso sistémico. Estudio clínico.

Se presentan los hallazgos clínicos y de laboratorio de 11 niños afectos de LE sistémico concluyéndose que estos son similares a los encontrados en grupos de edad mas avanzada aunque la malignidad sea mayor en los pacientes de edad corta. El número de varones y mujeres fué casi el mismo, lo cual señalaría la falta de predisposición de uno u otro sexo para contraer la enfermedad. Se encontraron, además de las lesiones consideradas como comunes a los adultos, colitis ulcerosa crónica, cirrosis hepática e hipertensión primaria. En todos los casos se encontró una marcada elevación de gamaglobulina, apareciendo en los pacientes con cirrosis hepática una fracción proteica extremadamente alta. El hecho de que aún pacientes con sindrome nefrótico, con eliminación urinaria aumentada de gamaglobulina, presentaran cifras altas de esta fracción, habla en favor de su intensa producción en el curso de la enfermedad. Se concluye que esta afección no es extremadamente rara en la infancia.

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The Danish Pediatric Society

Meeting, October 12, 1955

J. Vesterdal: **Goitre in a newly born infant.**

A full term female infant, aged 6 weeks, in whom a large goitre had been present since birth, was demonstrated. The infant was weak and could not suck. The respiration was somewhat stridorous and the infant occasionally became cyanotic. No sign of myxoedema was present. For the first 3 weeks, the infant was treated with iodine but without effect. Since then no treatment had been administered. The goitre was entirely unchanged and, as symptoms of compression were present, surgical treatment was considered.

Two factors may be of etiological significance:

(1) The mother suffers from asthma and was undergoing treatment with cortisone and ATCH at the period when conception occurred. It is, however, very improbable that this can have produced goitre in the foetus as probably no thyroid gland had developed so early in foetal life. If these substances had exerted any harmful effect they would more likely have caused abortion or severe deformity of the foetus.

(2) The mother was, in addition, suspected of suffering from hyperthyroidism during pregnancy but at that time no definite increase in the metabolic rate could be demonstrated and she was not treated with thiouracil or similar preparations during pregnancy. Following delivery, a definitely raised metabolic rate was observed in the mother.

In all probability, the goitre in the infant is connected with slight hyperthyroidism in the mother (transmission of thyreotropic hormone from the mother to the foetus?).

J. Lund: **Surgical urinary conditions in children. Treatment and results of treatment.**

Thirty-three cases of uro-genital conditions in children from the Copenhagen County Hospital in Gentofte were presented. The majority of the patients were treated in co-operation with the Pediatric Department of The County Hospital. Pyuria was the principal symptom which initiated urological investigation. In the County Hospital up to 50 per cent of the children with recurrent pyuria or pyuria resistant to therapy suffered from anatomical anomalies in the urinary tract. These anomalies consisted mainly of juxtapelvic stenosis of the ureter (10 cases), ureterocele (4 cases) and megaloureter (7 cases). The operative techniques and the post-operative results of treatment in these various conditions were reported and urological investigation was advocated in children when there is the slightest suspicion of anatomical anomalies in the urinary tract, i.e. pyuria which does not disappear promptly, abdominal pain

without other demonstrable cause together with anaemia and failure to thrive in cases where pathological conditions in other organs cannot be demonstrated.

(To be published in *Ugeskrift for Læger*.)

C. C. Winkel-Smith: **Two cases of ileo-cutaneous ureterostomy for complete incontinence of urine.**

Ileo-cutaneous ureterostomy is an intervention in which both ureters are anastomosed to an isolated loop of ileum which opens directly on to the surface of the body. The urine is collected here in a bag. The decisive stipulation in the choice of this method of operation at present must probably be that the anus is incompetent so that transplantation into the colon, which would otherwise have been the obvious solution, is excluded. The advantages of ureterostomy are to be found in the fact that the loop of ileum is completely isolated from the rest of the intestinal tract. Implantation of the ureters is therefore easier, hydronephrosis does not develop and, further, experience shows that hyperchloraemic acidosis, a not infrequent complication in colon anastomoses, is completely avoided in ureterostomy.

In the two cases which were presented, the indications for operation were ectopia of the bladder and myelocele, respectively. In the latter case, the post-operative course was uneventful. In the former case, severe disturbances of the electrolyte balance developed a couple of weeks after operation; these disappeared following appropriate therapy. The cause was probably a slightly constricted stoma, which produced a certain degree of retention of urine in the intestinal pouch.

J. Kringelbach: **Hyperostosis corticalis infantilis (Caffey's syndrome).**

Infantile cortical hyperostosis, first described by Caffey in 1945, is a disease which occurs in the first months of life. It is characterized by swelling of the soft tissues, irritability and periosteal new bone formation, frequently accompanied by pyrexia, raised BSR, anaemia and leucocytosis. The duration is from a few weeks to several months and the course of the disease is characterized by spontaneous remissions and exacerbations. The prognosis is favourable. Several factors suggest that it is an infectious condition but hitherto no agent has been demonstrated. Pathological changes in the arteries in the form of proliferation of the intima, have been demonstrated and some authors consider this to be the primary factor in the disease. The arterial defect is presumed to be hereditary. Therapy with ACTH and cortisone seems to be able to abbreviate the course of the disease.

A case history is recorded: A boy of over 4 months of age who had previously been healthy took ill acutely with pyrexia, irritability, soft tissue swelling of the thorax and caput, raised BSR, anaemia and leucocytosis. The illness was interpreted as sepsis and osteomyelitis, and treatment with penicillin, terramycin, achromycin and blood transfusions was instituted. The disease lasted for approximately 2 1/2 months and the course was undulating but the patient was discharged in good health and follow-up examinations one month and one year later showed normal conditions. It became evident later that the clinical picture corresponded closely to the available descriptions of infantile cortical hyperostosis. Re-examination of the X-ray photographs confirmed this diagnosis, cortical hyperostoses being found on several ribs and on the jaw. This case is the first to be published in Scandinavia.

Discussion.—*J. Vesterdal:* Demonstrated some X-ray photographs of a patient suspected to be suffering from Caffey's disease. The patient was a girl who from the

age of one year became weak, irritable and tender on the arms, legs and one mastoid process. Her gait became stiff. She was admitted to The Pediatric Department, The University Hospital, Copenhagen, at the age of 2 years and 5 months. Slight thickening of the second left metacarpal and of both tibiae was then observed. The ESR was greatly raised. No swelling of the liver, spleen nor lymphatic glands was present. Smears of peripheral blood and from bone marrow puncture were normal. On X-ray examination, the long bones were found to be thickened and plump with increased deposition of calcium, particularly in the distal segments. Some of the metacarpal and metatarsal bones were similarly singularly thickened and calcified. There were no changes in the jaw. Caffey's disease or hypervitaminosis A were first suspected but the case history rendered the latter condition improbable. On reviewing the X-ray photographs, the changes were considered to resemble leucaemic osseous changes. Despite careful investigation, no other sign of leucaemia could be found. In all probability, however, this disease is concerned.

J. Andersen: **A case of Wilson's hepato-lenticular degeneration.**

The patient was a boy aged 12 years who had been healthy until a year previously. During the past year, increasing rigidity, dysarthria and emotional instability had developed. Four attacks of haematemesis six weeks previously. The patient showed typical Kayser-Fleisher's ring. Neurological examination: extrapyramidal syndrome. Radiologically: oesophageal varices; apart from 7 per cent retention in the bromsulphalein test, liver tests were, however, normal. In addition, the serum copper was low: 34 γ %; increased copper excretion in the urine: 170 γ % per 24 hours; low serum iron: 43 γ % and thrombopenia. No enlargement of the liver nor spleen. No amino aciduria could be demonstrated by paper chromatography. Pathogenesis: abnormal copper retention in the organism is present on account of increased resorption and reduced secretion in the colon. Cases have been recorded in which negative copper balance and clinical improvement occurred on treatment with series of BAL and maintenance treatment with ion exchange resins orally. At present, the above patient is undergoing treatment with a new ion exchange resin which can absorb approximately 30 times as much copper per gram of resin as the polystyrene sulphonates previously employed.

Meeting, October 20, 1955

Professor W. G. Lennox: **Harward Medical School, Boston: Epilepsy in childhood.**

Meeting, December 1, 1955

1. *Kaj Tolstrup:* **Skinny children.**

   No report submitted.

2. *Ib Boesen:* **Demonstration of X-ray photographs with Philip's picture intensifying apparatus.**

3. *P. Plum:* **Impressions from a journey to Brazil.**

Acta Pædiatrica 45: 208—209. March 1956

BOOK REVIEWS

Book received.

Atlas und kurzgefasstes Lehrbuch der Phonokardiographie und verwandte Untersuchungsmethoden. K. Holldack and D. Wolf. Georg Thieme Verlag. Stuttgart. 1956. 171 pages, 179 figures. Price DM 49.50.

Die genuine Vitamin D-resistente Rachitis. Walter Swoboda. Wiener Beiträge zur Kinderheilkunde. Band VI. Verlag für Medizinische Wissenschaften. Wilhelm Maudrich. Wien and Bonn. 1956. 80 pages, 12 figures, 5 tables.

Rheumatoid Arthritis and Psoriasis Vulgaris. Tibor Benedek. Chicago Medical Book Company. Jackson and Honore Streets. Chicago 12, Ill. 1955.

Die Papierchromatographie in der Kinderheilkunde Horst Bickel and Fritz Souchon. Beihefte zum Archiv für Kinderheilkunde. No. 31. Ferdinand Enke Verlag. Stuttgart. 1955. Price DM 27.—

Les explorations biologiques en pédiatrie. Claude Polonovski and Jean Colin. Expansion Scientifique Française. Paris. 1955. 500 pages. Price 3.900.— fr.

Biologische Daten für den Kinderarzt. Joachim Brock. 2nd Edition. Two vol. Springer Verlag. Berlin, Göttingen, Heidelberg. 1954. 1834 pages, 255 figures. Price DM 75. + 125.—.

Die akute Poliomyelitis, ihre Ätiologie, Pathogenese, Klinik und Behandlung. R. Ch. Berend. Beiträge zur praktischen Medizin. No. 36. Ferdinand Enke Verlag. Stuttgart. 1955. 70 pages. Price DM 9.40.

Die kongenitalen Missbildungen, ihre Ursachen und Prophylaxe. Martin Wrete. Almqvist & Wiksell. Uppsala. 1955. 321 pages, 284 figures. Price Swed. cr. 40:—.

Pädiatrischer Röntgenatlas. K. H. Schäfer, M. A. Lassrich and R. Prevot. Georg Thieme Verlag. Stuttgart. 1955. 333 pages, 700 figures. Prince DM 115.—.

W. Heck: Die Klinik der congenitalen Angiocardiopathien im Säuglings- und Kleinkindesalter.

Gustav Fischer Verlag, Stuttgart. 1955.

123 cases of congenital heart disease in infancy form the basis of this study. 74 cases died, i.e. about 60 %. Only the post-mortem cases gave a correct diagnosis as catheterization and angiocardiography was never performed in infancy. The different malformations are described in the last part of the book. The post-mortem cases are presented in informative tables.

Pediatric Orthopedics.

Ped. Clin. N. Amer. 1955, Nov., 229 pages, 128 figures.

Several authors review different orthopedic problems, mainly those of the spine and lower extremities, in infants and children. Some chapters are rather specialized for the general pediatrician. In spite of unnecessary repetitions the book gives a good

and clear discussion of such topics as limp, knee lesions and foot deformities, which the pediatrician will meet in his office and in which an early diagnosis is of importance. The book demonstrates that much effective treatment can be given by the general pediatrician and the school-physician in his office and permanent disability can thus be prevented.

N. O. Ericsson

ANNOUNCEMENTS

I^er Congrès International de Pathologie Infectieuse
Lyon, 24–25–26 Mai 1956

Le 1^er Congrès International de Pathologie Infectieuse se tiendra à Lyon les 24, 25 et 26 Mai 1956, à la Faculté Mixte de Médecine et de Pharmacie, 8, Avenue Rockefeller. Les sujets à l'ordre du jour sont:

1° — *Les neuro infections virales* — Rapporteurs :

P^r Ramon (Paris) : La Rage — Epidémiologie — Immunologie — Prophylaxie.
P^r Pette (Hambourg) : Das Tierexperiment in der Erforschung neuroviraler Erkrankungen.
P^r D'Alessandro e Dott, L. Dardanoni (Palerme) : Aspetti etio-epidemiologici delle nevrassiti virali.
P^r Mollaret (Paris) : Les méningites récurrentes à ultra-virus.

2° — *Les maladies du collagène dans les infections* — Rapporteurs :

P^r Fanconi, et D^r E. Rossi (Zurich) : Le tableau clinique des maladies du collagène et l'importance étiopathogénique des maladies infectieuses bactériennes.
D^r Delaunay (Paris) : Les liaisons collagène muco-polysaccharides dans la trame conjonctive et leur importance dans le déclenchement des maladies du collagène.

En outre, à l'occasion du congrès, un Colloque sur la Rage se tiendra le Vendredi 25 Mai, à 15 h 30, sous la présidence du D^r Remlinger; il portera sur les sujets suivants: sérum antirabique — virus Flury — projets de convention sanitaire internationale.

Le Dimanche matin 27 Mai à 9 h : — Une séance de la Réunion Lyonnaise de Pédiatrie, à la Clinique Médicale Infantile, Hôpital Edouard Herriot.

Acta Pædiatrica 45: 211—221. May 1956.

From the Pediatric Department, University of Oslo
(Chief: Professor LEIF SALOMONSEN)

Blood Gas Determinations on Premature Infants

III. Investigations on Premature Infants with Recurrent Attacks of Apnea

by WILHELM BLYSTAD

Through gas analyses of cutaneous blood the author has tried to arrive at a functional evaluation of the respiration of premature infants. The laboratory methods, the results obtained on premature infants without respiratory complications, and the results for infants suffering from early neonatal dyspnea (the Hyaline Membrane Syndrome) have been reported in two earlier publications. The present article deals with investigations carried out on premature infants with recurring attacks of apnea.

Attacks of apnea represent a frequent and most serious complication where premature infants are concerned. The etiologic and pathogenetic background for these attacks is uncertain. It has been maintained that the attacks of apnea are due to a failure in the central regulation of the respiration (Essbach and Peiper). It is not yet clear whether anatomic, cerebral changes involving a more permanent depression of the respiratory center form the basis of the acute respiratory failure during the attacks. It was hoped that the present investigations would give an answer to this question. The sampling has consequently been carried out in the free intervals between the attacks.

Premature infants show a marked tendency to irregular respiration, and periodic breathing is a frequent occurrence (Smith). A clear distinction between the relatively brief attacks of apnea occurring in periodic breathing and the more serious attacks is hardly possible. Rossier maintains that attacks of apnea lasting more than 2 minutes indicate a severe pathologic background. The patients examined in this study have all suffered several attacks of apnea, each lasting at least 2 minutes.

The laboratory methods have been described in an earlier publication (Blystad). The limitation of the method with regard to the O_2 determinations has to be pointed out. The method gives exact information only where

hypoxemic conditions are concerned. If the O_2 saturation of the blood is high, and the O_2 tension lies above 65 mm Hg, the results obtained will be too low.

Materials

Analyses have been carried out on 10 premature infants suffering from attacks of apnea. The clinical data is summarized as follows:

The birth weight ranged from 920–2580 g, averaging 1370 g. The facts concerning pregnancy and delivery are found in Table 1.

The attacks of apnea lasted from 2–3 minutes up to about half an hour. The chart below indicates the time (day of life) of occurrence at the attacks.

Case	3:	1 – 1
„	5:	2 – 2
„	7:	21 – 22 – 24 – 24
„	8:	12 – 12
„	11:	2 – 6 – 6 – 7 – 23 – 25
„	16:	2 – 3 – 4 – 22 – 22
„	18:	2 – 6 – 6 – 6
„	22:	1 – 1 – 1 – 2 – 2 – 2 – 3 – 3 – 3
„	23:	2 – 2
„	28:	1 – 1

It has been found advantageous to classify the recorded attacks of apnea in three main groups.

1. Attacks of apnea occurring in the course of an early neonatal dyspnea. Three of the infants which were examined suffered from these two types of respiratory complications. The attacks of apnea were relatively brief in these cases, lasting from 2–3 minutes. All three of the patients died, and the autopsy revealed massive atelectases and hyaline membranes in the lungs.

2. Attacks of apnea which occurred in the course of the first four days of life. In these cases neither early neonatal dyspnea nor definite lung complications were present. Analyses were carried out on five infants. It was characteristic of these cases that the condition seemed satisfactory before and between the attacks. The respiration seemed effortless, and the color was good during oxygen administration. The attacks of apnea occurred suddenly and unexpectedly. After the attacks the patients seemed somewhat listless, however, and the muscular tone was reduced.

One of these patients (Case 23) died during an attack of apnea, 36 hours after birth. The autopsy revealed scattered areas of atelectases, but no hyaline membranes in the lungs. The four other patients survived.

3. Attacks of apnea occurring later, after the fourth day of life. Such attacks were recorded for five of the infants in this material. In these cases symptoms of a respiratory infection had developed. There were increased secretions in the pharynx. The color was often greyish, and at times a tendency to cyanosis was observed. The respiration seemed somewhat labored, with inspiratory retractions. Fine rales were found over the lungs. In four of these patients the symptoms disappeared in the course of a couple of days. In one case a pneumonic condition developed. X-ray examinations revealed

TABLE 1

Complications of pregnancy and birth in 10 premature infants who suffered from attacks of apnea.

	Birth weight in g	Complications of pregnancy	Birth complications	Initiation of respiration
Case 3	1650	–	Premature rupture of the membranes. Breach	Some cyanosis
Case 5	2580	–	Induction	Some cyanosis
Case 7	1310	–	–	–
Case 8	1260	–	Premature rupture of the membranes. Forceps	–
Case 11	1090	–	–	–
Case 16	1350	Mild hemorrhage	Premature rupture of the membranes	Some cyanosis
Case 18	1160	Hydramnios?	–	–
Case 22	920	Hydramnios?	Breach	–
Case 23	1090	Mild hemorrhage	Prolonged labour	–
Case 28	1300	–	–	–

densities in the lungs of two of the patients, while the findings in the two other cases were uncertain. All the patients survived.

All the patients received incubator treatment. The oxygen administration was 3–6 l per minute. For the surviving patients the oxygen therapy was kept up from 5–8 weeks. The respiratory infections were treated with penicillin or aureomycin. Secretions in the pharynx were repeatedly drained out.

In order to reestablish the respiration in cases with apnea cutaneous stimulation was tried first. The introduction of a catheter in the nose or pharynx for aspiration also seemed an effective stimulus. After prolonged attacks of apnea, artificial respiration had to be carried out.

Results

1. *Analyses carried out on three premature infants who had attacks of apnea in the course of an early neonatal dyspnea.* The results are found in Table 2. A marked rise in the CO_2 tension, an accentuation of the metabolic acidosis, and very low values for the blood pH were found in these cases. The O_2 tension was low, and indicated a rather pronounced hypoxemia.

2. *Analyses carried out on five infants who had attacks of apnea in the course of the first four days of life, and where no definite pulmonary complications were present.* These results are recorded in Table 3. A comparison between these results and those obtained on premature infants without respiratory complications (Table 4) reveals no pronounced displacement of the

Table 2

Analyses carried out on three premature infants who had attacks of apnea in the course of an early neonatal dyspnea. The attacks were relatively brief, lasting from 2–3 minutes. The patients died, and autopsy revealed atelectases and hyaline membranes in the lungs.

	Age	O_2 tension mm Hg	CO_2 tension mm Hg	CO_2 content volumes per cent	pH
Case 3	7 hours	47.2	70.4	56.4	7.14
	8½ „	21.4	71.9	47.3	7.05
Case 5	44 „	23.9	63.9	34.8	6.95
	46 „	21.6	66.5	32.7	6.90
Case 28	3 „	45.6	91.7	58.2	7.03
	6 „	25.9	157.5	51.9	6.69
	7 „	15.7	92.0	42.5	6.87

Table 3

Analyses carried out on five premature infants who had attacks of apnea in the course of the first four days of life. There was no indication of serious pulmonary complications in these cases. In one case (Case 22, first day), the sampling was carried out immediately after an attack of apnea. The other samples were taken from half an hour to several hours after the attacks.

	Age	O_2 tension mm Hg	CO_2 tension mm Hg	CO_2 content volumes per cent	pH
Case 11	4 days	59.8	39.7	46.8	7.32
	4 „	65.3	42.4	48.9	7.32
Case 16	2 „	53.4	42.0	49.9	7.32
	3 „	57.8	45.3	47.8	7.27
Case 18	2 „	56.8	40.1	45.0	7.30
	2 „	52.5	37.4	41.3	7.29
Case 22	1 „	58.9	51.8	49.6	7.23
	3 „	64.0	38.5	41.2	7.28
	4 „	75.0	37.5	45.8	7.34
Case 23	2 „	51.8	41.3	48.6	7.32
	2 „	55.2	39.7	46.5	7.32
		Average	41.4	46.5	7.30

TABLE 4

Analyses carried out in the course of the first four days of life on premature infants who showed no symptoms of respiratory disturbances.

	Age	O_2 tension mm Hg	CO_2 tension mm Hg	CO_2 content volumes per cent	pH
Case 2	4 days	63.8	36.6	42.7	7.32
Case 4	1 „	64.9	45.8	50.2	7.29
	2 „	62.7	37.5	50.4	7.38
	3 „	56.1	33.2	50.2	7.44
Case 9	1 „	54.1	37.0	53.2	7.41
	2 „	63.3	35.2	44.1	7.35
	4 „	61.5	44.4	51.5	7.33
Case 10	1 „	51.4	45.6	51.9	7.30
	1 „	53.8	44.8	52.5	7.32
	2 „	59.0	36.8	43.4	7.32
	4 „	73.9	28.9	40.2	7.32
Case 12	2 „	76.4	36.6	44.8	7.34
	3 „	73.7	41.0	52.0	7.35
Case 13	1 „	50.1	34.4	44.1	7.36
	4 „	59.2	36.4	52.5	7.42
Case 17	1 „	68.1	32.5	43.3	7.37
	4 „	78.0	39.5	53.6	7.39
Case 20	2 „	54.5	42.7	53.3	7.35
Case 21	4 „	71.1	42.2	51.8	7.34
		Average	38.5	48.7	7.35

values. The average CO_2 tension lies at a slightly higher level, and the average values for the CO_2 content in plasma and for the pH lie at a slightly lower level for the patients suffering from attacks of apnea. These differences are not statistically significant, however. The O_2 tensions, too, were in fairly good agreement with the values obtained on infants without respiratory complications. The results did not indicate the presence of any severe hypoxemia.

3. *Analyses carried out after the fourth day of life on premature infants with attacks of apnea.* — Repeated determinations were carried out on six of these patients in the course of a fairly long period. The results are recorded in Figures 1, 2, and 3.

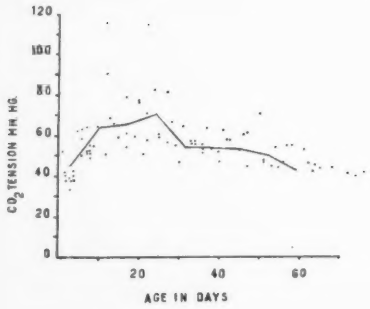

Fig. 1. Co_2 tensions of cutaneous blood in premature infants who had recurrent attacks of apnea. The samples have been obtained in the intervals between the attacks, and during the first weeks after the tendency to apnea had subsided.

As will be seen, the results obtained in the course of the first days after birth lie within the spread of the values for premature infants without respiratory disturbances. However, around the end of the first week of life an increase of the CO_2 values set in. Evidence of an increased CO_2 tension for the different patients was first found on the 5th, 6th, 7th, 8th, 9th day of life respectively. One patient was first examined on the 25th day of life, and an increased CO_2 tension was found in this case too.

In all cases this respiratory acidosis persisted for several weeks. The maximum values for the CO_2 tensions for the various patients ranged from 57.1–115 mm Hg. The maximum values for the CO_2 content in plasma ranged from 63.8–87.0 volumes per cent.

The increased CO_2 values were not only demonstrated in connection with the attacks of apnea, but persisted long after these had subsided. The length of the period of respiratory acidosis for these patients varied between five and eight weeks.

The results for the blood pH in the periods of increased CO_2 values mostly ranged from 7.20–7.35, averaging 7.28. The average for premature infants without respiratory disturbances was 7.36. This difference is statistically significant.

The results for the O_2 tensions show a fairly wide spread. At the onset of the respiratory acidosis the O_2 analyses tend to give relatively low values.

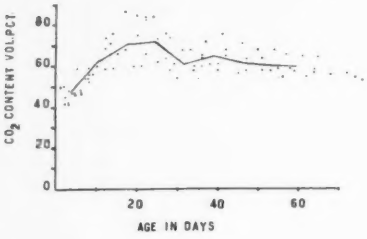

Fig. 2. Plasma Co_2 contents in 6 premature infants who had recurrent attacks of apnea.

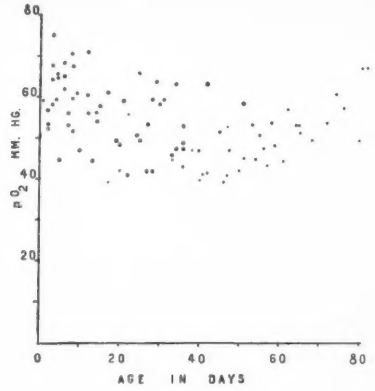

Fig. 3. O_2 tensions of cutaneous blood in 6 premature infants who had recurrent attacks of apnea. Circles indicate samples obtained during O_2 administration. Dots indicate samples taken while breathing atmospheric air. Results above 65 mm Hg are inaccurate, i.e., too low.

In the periods of increased CO_2 values the O_2 tension lies below 50 mm Hg in 50 per cent of the analyses. For premature infants without respiratory disturbances the spread ranged from 50.1–82 mm Hg.

Comments

According to the clinical conditions and the laboratory results a classification of the material in three groups has been made:

1. In the *first group* are included infants who had attacks of apnea occurring in the course of an early neonatal dyspnea. In these patients were found: a marked respiratory acidosis, an accentuation of the metabolic acidosis, very low values for the blood pH, and a rather pronounced hypoxemia.

Similar results have previously been reported for infants who suffered from early neonatal dyspnea, but who had no attacks of apnea. There is reason to believe that these changes are principally due to a respiratory failure of pulmonary origin. The clinical examination of these patients showed increased respiratory efforts before and after the attacks. This seems to indicate that the respiratory center gave an adequate response, and thus was relatively intact except during the attacks. The attacks of apnea were relatively brief, and occurred in the course of the disease as acute crises of respiratory failure.

It is possible that the attacks of apnea were secondary to the asphyxia caused by pulmonary changes. Hypoxemia, CO_2-retention, or acidemia can have been the factors causing the attacks. All three of the patients died.

In the author's experience the occurrence of attacks of apnea in the course of an early neonatal dyspnea represents a very grave prognostic sign.

2. In the *second group* are included infants who had attacks of apnea in the course of the first four days of life, but where no definite pulmonary complications were demonstrated. The results of the analyses did not differ greatly from the values for premature infants without respiratory disturbances. Thus, they gave no indication of a permanent depression of the respiratory center which would explain the tendency to attacks of apnea. After the attacks the ventilation was sufficient to correct the accumulation of carbon dioxide which had taken place during the apnea. The attacks seemed to occur as acute crises in the regulation of the respiration. No conclusion can be drawn from the present investigations with regard to the pathogenesis of these crises.

It seems evident that the conditions under which the attacks of apnea occur can vary. If pulmonary pathologic changes are present the prognosis is very poor. In cases who had no severe pulmonary complications the respiratory situation and the immediate prognosis were considerably better.

3. The *third group* includes infants who had attacks of apnea after the fourth day of life. The material consists of five infants. In these cases the results presented a fairly uniform and characteristic picture, inasmuch as all the patients developed a respiratory acidosis and a tendency to hypoxemia. The respiratory acidosis was present not only in connection with the attacks of apnea. It occurred at about the end of the first week of life, and persisted long after the attacks had subsided. Corresponding, characteristic changes were also observed in a sixth infant, who had attacks of apnea during the first three days of life, but not later.

The author has been in doubt with regard to the interpretation of these changes. It seems probable that central as well as pulmonary factors would be of significance in the pathogenesis.

In one case the respiratory acidosis seemed to be chiefly of pulmonary origin. This infant developed a protracted pneumonic condition. The clinical recovery was accompanied by a gradual regression of the symptoms of respiratory failure. The other infants also developed symptoms indicating a respiratory infection. The symptoms were here considerably less pronounced and of short duration. In spite of this, it is possible that pathologic changes in the respiratory tract may have contributed in establishing the respiratory acidosis.

However, for five of these infants evidence of respiratory failure was found in long periods where the respirations were calm, effortless and partly periodic. It was evident that a depression of the respiratory center had developed. The mechanism is uncertain here. It seems probable that in-

creased CO_2 tensions are primarily brought about by the attacks of apnea and by pulmonary factors. An adaptation of the respiratory center to these increased tensions has subsequently taken place. Evidence of an adaptation of the respiratory center to increased CO_2 tensions has been found in adult patients suffering from chronic lung diseases (Comroe and co-workers, Hillen, Storstein). It can hardly be decided with certainty whether or not this depression of the respiratory center is a cause of the attacks of apnea which occurred late.

Howard and Bauer (1949, 1950) maintained that in premature infants there is a connection between periodic breathing and a low CO_2 production. Because of a partially anaerobic metabolism the production of carbon dioxide should be low, and they were of the opinion that the CO_2 stimulation of the center was insufficient. However, the present investigations show that low values of carbon dioxide in the blood are not a precondition for this type of respiration. Periodic breathing has frequently been observed in cases with respiratory acidosis. In these infants it seems natural to consider the periodic breathing a result of the depression of the respiratory center.

Summary

Blood gas analyses of cutaneous samples obtained from premature infants have been carried out. The results obtained on 10 infants suffering from recurrent attacks of apnea are reported. The classification of the material falls into three groups:

1. In three infants who had attacks of apnea occurring in the course of an early neonatal dyspnea (the Hyaline Membrane Syndrome) were found: an increased CO_2 tension, an accentuation of the metabolic acidosis, markedly reduced values for the blood pH, and low values for the O_2 tension indicating a rather severe hypoxemia. There is reason to believe that these changes are chiefly due to a respiratory failure of pulmonary origin. It is possible that the attacks of apnea are secondary to the asphyxia caused by pulmonary changes. The three patients died.

2. The results obtained on five infants who had attacks of apnea in the course of the four first days of life, but who did not suffer from early neonatal dyspnea, did not differ greatly from the values found for premature infants without respiratory complications. Thus, in the free intervals between the attacks, there was found no evidence of a depression of the respiratory center which would explain the tendency to attacks of apnea.

3. In six surviving infants, five of whom had attacks of apnea later in the course, a respiratory acidosis and a tendency to a moderate hypoxemia gradually developed. These changes were not only present in connection with the attacks of apnea, but persisted long after these had subsided, in periods of calm and effortless respiration. It is probable that pulmonary changes as well as a central depression of the respiration are involved in the pathogenesis of this respiratory acidosis.

Periodic breathing was often observed in infants where the analyses showed a respiratory acidosis. Low values for carbon dioxide in the blood do not constitute a precondition for the occurrence of this type of breathing in premature infants.

Détermination des gaz dans le sang de nourrissons prématurés. III. *Recherches chez des nourrissons prématurés présentant des accès répétés d'apnée.*

L'auteur a analysé les gaz contenus dans des échantillons de sang cutané chez des prématurés. On rapporte les résultats obtenus chez dix nourrissons ayant des accès répétés d'apnée. Les patients peuvent être répartis en trois groupes: On a trouvé chez trois nourrissons ayant eu des accès d'apnée au cours d'une dyspnée néonatale précoce (le syndrome de membranes hyalines) une tension de CO_2 augmentée, une accentuation de l'acidose métabolique, des valuers fortement réduite pour le pH sanguin et des valeurs basses pour la tension d'oxygène indiquant une hypoxémie assez importante. Il y a des raisons de croire que ces changements sont principalement dûs à une insuffisance respiratoire d'origine pulmonaire. Les trois patients sont morts. Les résultats obtenus chez cinq nourrissons ayant eu des accès d'apnée au cours des quatre premiers jours de la vie, mais n'ayant pas souffert d'une dyspnée néonatale précoce, ne différaient pas fortement des chiffres trouvés ches des prématurés sans complications respiratoires. On n'a ainsi pas trouvé, pendant l'intervalle libre entre les accès, de signe d'une dépression du centre respiratoire, qui pourrait expliquer la tendance aux accès d'apnée. Chez six nourrissons survivants, dont cinq ont présenté des accès d'apnée pendant la période ultérieure, il s'est développé graduellement une acidose repiratoire et une tendance à l'hypoxémie modérée. Ces changements existaient non seulement pendant les accès d'apnée, mais persistaient longtemps après que ceux-ci avaient cessé, pendant des périodes de respiration calme et sans effort. Il est probable que des modifications pulmonaires ainsi qu'une dépression centrale de la respiration interviennent dans l'acidose respiratoire. On a souvent remarqué une respiration périodique chez des nourrissons chez lesquels les analyses montraient une acidose respiratoire. Un taux de CO_2 bas dans le sang n'est pas une condition indispensable pour le développement de ce type de respiration chez des nourrissons prématurés.

Blutgasbestimmungen bei Frühgeburten. — III. *Untersuchungen an Frühgeburten mit gehäuften apnoischen Anfällen.*

Es sind Gasanalysen aus Kapillarblut bei Frühgeburten durchgeführt worden. Über die Ergebnisse, die bei 10 an gehäuften Anfällen von Apnoe leidenden Kindern erlangt wurden, wird berichtet. Die Einteilung des Materials zerfällt in drei Gruppen: Bei drei Kindern, die im Verlauf einer frühzeitigen Neugeburtsdyspnoe apnoische Anfälle hatten (Syndrom der hyalinen Membranen), wurde folgendes gefunden: eine erhöhte CO_2-Spannung, eine Akzentuierung der Stoffwechselacidose, deutlich reduzierte Werte des Blut pH und niedrige Werte der O_2-Spannung, was eine ziemlich schwere Hypoxaemie anzeigt. Es ist begründet anzunehmen, dass diese Veränderungen hauptsächlich durch ein pulmonales Versagen der Atmung hervorgerufen sind. Es ist möglich, dass die apnoischen Anfälle der durch pulmonale Veränderungen hervorgerufenen Asphyxie untergeordnet sind. Die drei Patienten starben. — Die Ergebnisse bei fünf Kindern, die im Laufe der ersten vier Lebenstage Anfälle von Apnoe hatten, aber nicht an Neugeborenendyspnoe litten, unterschieden sich nicht wesentlich von den Werten, die bei den Frühgeburten ohne Atemkomplikationen gefunden wurden. Daher findet man in den freien Intervallen zwischen den Anfällen keinen Hinweis auf die Drosselung des Atemzentrums, der die Tendenz zu apnoischen Anfällen erklären könnte. Bei sechs überlebenden Kindern, von denen fünf im späteren Verlauf Anfälle von Apnoe hatten, entwickelte sich allmählich eine respiratorische Acidose und eine Tendenz zu einer mässigen Hypoxaemie. Diese Veränderungen bestanden nicht nur

in Verbindung mit apnoischen Anfällen, sondern hielten lange nach Abklingen derselben in Perioden ruhiger und müheloser Atmung an. Es ist wahrscheinlich, dass Lungenveränderungen sowie zentrale Beeinträchtigung der Atmung in die Pathogenese der respiratorischen Acidose verwickelt sind. Periodische Atmung wurde bei Kindern, bei denen die Untersuchungen eine respiratorische Acidose ergaben, oft beobachtet. Niedrige CO_2-Werte im Blut sind keine Vorbedingung für das Auftreten dieses Atemtyps bei Frühgeburten.

Determinación de gases sanguíneos en prematuros. — III. *Investigación en prematuros con ataques recurrentes de apnea.*

Se analizaron los gases en la sangre periférica de 10 prematuros con ataques recurrentes de apnea. El material se clasificó en tres grupos: En tres niños que tuvieron ataques de apnea durante el curso de una disnea neonatal temprana se encontró: aumento de la tensión de O_2, acentuación de la acidosis metabólica, marcada reducción en el pH sanguíneo y bajos valores en la tensión de O_2 indicando severa hipoxemia. Hay razones para creer que estos cambios son debidos principalmente a falla respiratoria de origen pulmonar. Es posible que los ataques de apnea sean secundarios a la asfixia causado por los cambios pulmonares. Tres pacientes murieron. Los resultados obtenidos en 5 casos que presentaron ataques de apnea en el curso de los primeros cuatro dias de vida pero no presentaron disnea temprana posnatal no difieren mayormente de los valores encontrados en prematuros sin complicaciones respiratorias. Durante los intervalos libres de ataques no se encontró evidencia de depresión del centro respiratorio que explicase la tendencia a dichos ataques. En seis sobrevivientes, cinco de los cuales tuvieron ataques tardíos de apnea, se desarrolló una acidosis respiratoria y una moderada tendencia a la hipoxemia. Estos cambios no estuvieron en conexión solo con los ataques de apnea sino que existieron sin ésta aun en períodos de calma y respiración tranquile. Esto probablemente se deba a que tanto cambios pulmonares como depresión respiratoria central forman parte de la patogenia de esta acidosis respiratoria. Respiración periódica fué observada en niños cuyo estudio reveló una acidosis respiratoria. Los bajos niveles de dioxido de carbono no son una precondición para que este tipo de respiración ocurra en el prematuro.

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CASE REPORT

Lymphosarcoma in an Infant, with Unusual Cutaneous Manifestations

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This communication describes a case of lymphosarcoma, with unusual cutaneous manifestations, in an infant.

Case Report

J. C., a one year old white female, had been well until about six weeks prior to her first University of Virginia Hospital admission. At that time her parents noticed several non-tender, reddish nodules on the infant's scalp. Since these apparently caused no discomfort, they were not thought to be serious. Within a few days other nodules were noted on the head and on the back, and within two weeks similar lesions appeared on the arms, legs, and trunk.

The child developed an upper respiratory infection some three weeks after the appearance of the nodules and an anemia was detected by her physician. She was started on antibiotics for the respiratory infection and was transfused because of the anemia. Following transfusion there was some degree of involution of the cutaneous lesions, but they soon reappeared. In addition, an opacity of the left cornea and swelling of the left eye were noted at about the same time.

In spite of the antibiotic therapy, the child continued to run a febrile course and for several days preceding her admission to this hospital she had become more irritable and her fever increased. She was referred to the University of Virginia Hospital on January 18, 1955.

In the birth history it was learned that the child's left eye had been injured during a home forceps delivery. There were also reported to have been some "knots" on the child's abdomen at three months of age and these were said to have been "just like the ones she has now". These lesions disappeared spontaneously. The growth, developmental, dietary, and past medical histories were non-contributory.

The laboratory work showed a urine with a trace of albumin, four to five white cells and four red cells per H.P.F., and uric acid crystals. The hemoglobin was 6 g %, and the hematocrit 16 %. The white blood count was 6700 per cmm; the differential count showed 10 large lymphocytes, 87 small lymphocytes, 2 monocytes, and 1 eosinophile. The tuberculin test and serological tests for syphilis were negative. The bone marrow was hypoplastic and the predominant cell was of a type which could not be definitely identified but which bore a general resemblance to that of a reticular cell found in lymphosarcoma.

On physical examination the child was found to be a well developed and adequately nourished white female of about nine months of age. She appeared quite ill and was

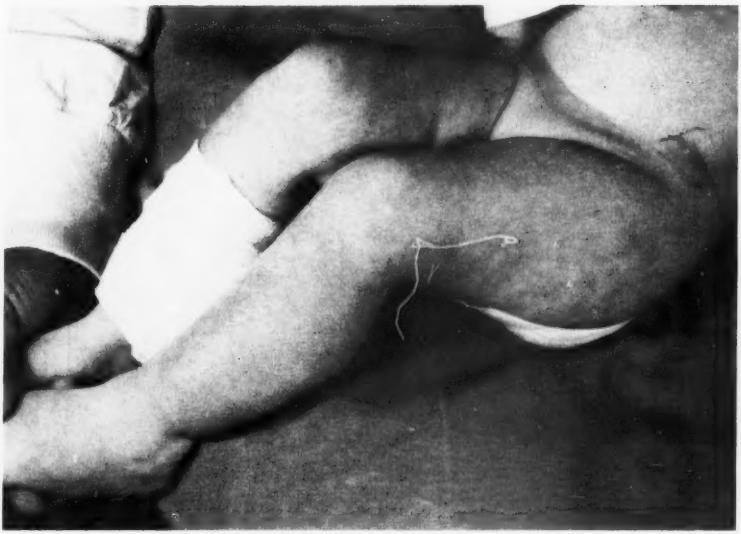

Fig. 1. Lymphosarcoma, showing infiltrated, nodular lesions of the skin.

very restless and irritable. The temperature was 38.9 C rectally and the respirations increased. The examination of the skin of the scalp, shoulders, arms, legs, dorsa and soles of the feet showed widespread and deeply infiltrated nodular lesions which were of a stony hard consistency, and which on pressure revealed a deeply violaceous color (Fig. 1). These lesions varied in size from 0.5 to 2 cm in diameter. There was no exfoliative element. A subcutaneous, well circumscribed, 2 × 2 cm abscess was present on the left buttock. The only palpable lymph nodes were shotty nodes in the inguinal region. Examination of the eyes showed discoloration of the left iris, and a cloudy left anterior chamber which seemed to have cells floating within. In addition, there was a white mass which appeared to arise from the angle of the anterior chamber. The lungs were normal and the heart showed only a moderate sinus tachycardia. Examination of the abdomen failed to reveal a palpable liver, spleen, or masses. The remainder of the physical examination was not significant.

During the ensuing days all observers were impressed by the fact that many lesions were constantly changing in size; some disappeared while others became smaller or larger.

On the fourth hospital day biopsies were taken from several nodules on the skin, an axillary lymph node was removed, and an incision and drainage of the buttock abscess was performed. Cultures from the abscess were negative.

Microscopic examination of the skin tumors (Fig. 2 and 3) showed a dense to moderately dense infiltrate which occupied the entire thickness of the dermis and which extended in some areas into the subcutaneous tissue. The infiltrate was comprised of a mixture of reticuloendothelial cells, lymphoblasts and occasional lymphocytes. The involved lymph nodes were replaced in variable measure by a similar neoplastic infiltrate. The pathologic diagnosis was lymphosarcoma.

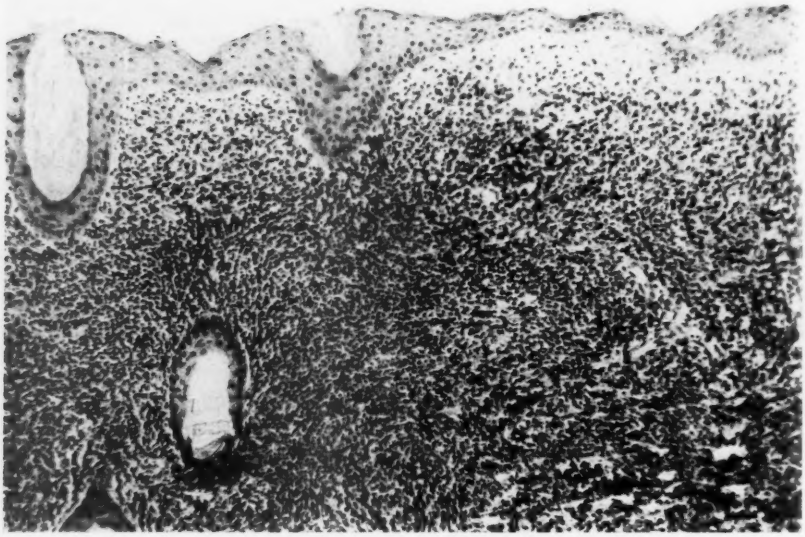

Fig. 2. Low power view of a biopsy specimen from the scalp showing the moderately dense infiltrate which extended through the entire thickness of the dermis.

Roentgen therapy was begun and the patient seemed to improve. The area of irradiation was extended until depression of the white count precluded further such treatment. She had received a total of 100 r to both sides of the head and 250 r to both anterior and posterior aspects of the lower extremities.

The child's course seemed one of progressive decompensation in spite of all measures. She developed a *Pseudomonas aeruginosa* infection in the buttock abscess and later a septicemia of the same organism. This septicemia was successfully treated with polymyxin only to have the patient develop a *Streptococcus fecalis* septicemia which slowly responded to chloroamphenicol therapy. She was taken home from the hospital by her parents where she remained for two months. About five days before her final admission she began to deteriorate very rapidly. Upon re-admission, the physical examination showed the same findings that were present upon the first admission, plus edema of the eyelids, moderate exopthalmos, marked hypertrophy of the gums, and a palpable liver and spleen. The only significant change in the laboratory work was a hematocrit of 26 % and a white count of 4800 with a differential of 60 lymphoblasts and 40 small lymphocytes. X-rays on admission failed to show evidence of lung or bone involvement. The patient was given one transfusion of packed blood cells and one X-ray treatment but her condition continued to worsen and she expired on the third hospital day. Permission for autopsy was refused.

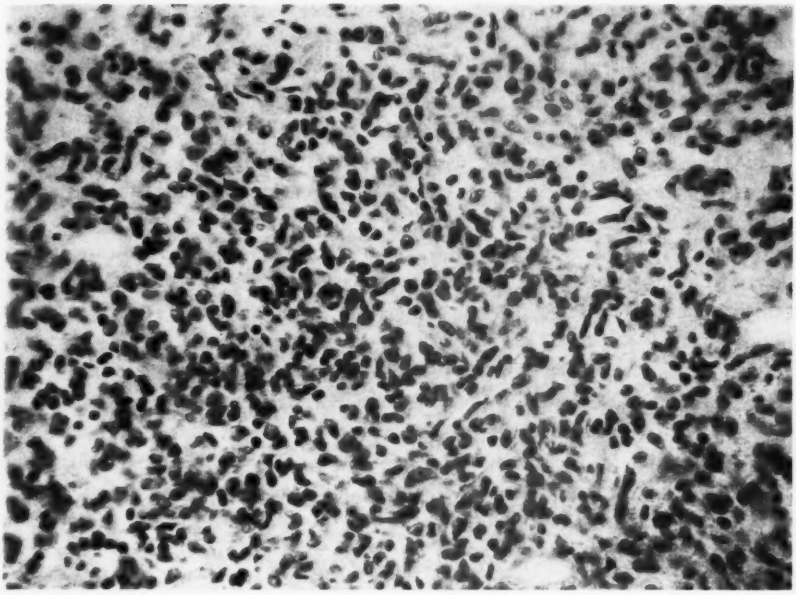

Fig. 3. High power view of the dermal infiltrate, which was comprised of a mixture of reticuloendothelial cells, lymphoblasts and occasional lymphocytes.

Discussion

The incidence of lymphosarcoma is low, being estimated at about five per cent of all malignant tumors, the most commonly affected age group is between 30 and 40 years. In the pediatric ages, lymphosarcoma has been reported to occur in early infancy, but the usual time of appearance would appear to be between five and ten years. Various estimates of the pediatric incidence have been made but most authors generally agree that lymphosarcoma is uncommon in children. In a group of forty-seven patients with lymphosarcoma reported by Howes *et al.* (1), 10 per cent occurred in children, while Dargeon (2) found an incidence of five per cent in a twenty-four year survey of all malignant tumors in children treated at Memorial Center in New York City. At the University of Virginia Hospital from July 1, 1951 through July 31, 1955 there were thirty-five patients with malignant tumors admitted to the pediatric service. A definite diagnosis of lymphosarcoma was made in seven of these cases and a probable diagnosis of lymphosarcoma made in two cases, giving a corrected incidence of 20 per cent. Of the diagnosed cases of lymphosarcoma, one had pathologically proven skin infiltra-

tion and two others showed skin lesions which were undoubtedly related to the lymphosarcoma but not histologically proven.

Since Kundrat (3) first recognized lymphosarcoma to be an entity separate from the aleukemic lymphomas, there has been considerable turmoil over what conditions should be placed in this category. The classification adhered to by the authors is that used by Dargeon which includes only those tumors of the lymphocytic or reticulum cell type. It is realized that no classification predicated without knowledge of etiology is entirely satisfactory.

Clinically, the skin lesions of lymphosarcoma may simulate any known dermatologic disorder and are therefore not diagnostic of this condition. Solitary or multiple nodules or papules are among the more frequent cutaneous manisfestations. Pruritus, with or without skin lesions, may call attention to the underlying process, while other less frequent manifestations include exfoliative dermatitis or erythroderma (4, 5), lichenification, atrophy, hyperkeratosis, and pigmentation.

Of particular significance in this case is the observation that the cutaneous tumors were extremely variable in their course. Many of these lesions exhibited remarkable growth patterns. Some lesions changed rapidly in size, even to the point of disappearance.

Historically, in this case, many lesions of the skin were initially present on the abdomen at three months of age and disappeared spontaneously. Similar lesions again showed an evanescent quality following blood transfusion before admission to the hospital. Later, this phenomenon was again observed here before any treatment was instituted. The evanescent character of the cutaneous lesions of lymphosarcoma is not an original observation by the authors, but it is a finding which bears reiteration.

Summary

A case of lymphosarcoma showing extensive cutaneous involvement in a nine month old female is described. The ephemeral character of the skin tumors in this case was notable.

Lymphosarcome chez un enfant avec manifestations cutanées inhabituelles.

Description d'un cas de lymphosarcome, chez un enfant de sexe féminin, agé de neuf mois, avec développement cutané important. Dans ce cas, le fait remarquable est que les tumeurs cutanées n'ont eu qu'un caractère éphémère.

Lymphosarkom bei einem Säugling mit ungewöhnlichen Hautmanifestationen.

Es wird ein Fall von Lymphosarkom mit ausgedehnter Beteiligung der Haut bei einem 9 Monate alten weiblichen Säugling berichtet. Der ephemerische Character der Hauttumoren in diesem Fall war beachtenswert.

Linfosarcoma con raras manifestaciones cutáneas.

Se describe el caso de una niña de 9 meses que presentaba extensas afecciones cutáneas además de un linfosarcoma. El hecho notable fué el caracter efímero de los tumores cutáneos.

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Galactose Intolerance: Observations on an Experimental Anima

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Intolerance to galactose has not long been separated from a confusing number of causes of failure to thrive in infancy.

Since von Reuss in Austria, Mason and Turner in America, and Bray, Isaac and Watkins in the United Kingdom, described their first experiences with the condition, information has accumulated to show that intolerance to galactose exhibits itself as a syndrome with a remarkably constant pattern. The outstanding features of this syndrome are failure of physical and mental development, cirrhosis of the liver and cataract formation in association with galactosaemia, galactosuria and aminoaciduria.

Göppert was first to notice a familial incidence in the disease. His observations have since been substantiated by a number of observers (Bell, Blair, Lindsay and Watson, Donnell and Lann, Cox and Pugh). Holzel and Komrower recorded the first case of an offspring of a consanguineous marriage.

Adequate descriptions of the clinical and biochemical findings are found in the above and later papers, Bruck and Rapoport, Donnell and Lann, Cox and Pugh and Mortensen and Søndergaard, but up to the present little was known about the mechanism by which galactose intolerance produces the profound physical disorder.

Raised levels of galactose in the blood after feeding diets containing lactose, and its excretion in the urine, suggest that the tissues of galactose intolerant individuals are unable to utilise galactose. It has been proposed that inability to utilise galactose is due to a block in its conversion to glucose. Arthurton and Meade have suggested that the block occurs either at the stage of galactose phosphorylation by galactokinase, or at the stage of the conversion of galactose-1-phosphate to its glucose isomer.

Recent work by Schwarz, Golberg, Komrower and Holzel has shown that red blood cells from patients with galactose intolerance accumulate galactose-1-phosphate. After feeding galactose these effects are even more pronounced and cells incubated in a galactose medium accumulated galactose-1-phosphate, but not glucose-1-phosphate. These results suggest that red cells from these patients have a restricted ability to convert galactose-1-

phosphate to glucose-1-phosphate. These observations represent the first step towards a more precise definition of the biochemical blockage.

Our first experience with the disease was in 1951 when a child with indeterminate failure to thrive was shown to have galactosuria and a diabetic type of blood sugar curve after the administration of galactose. A sibling who died in 1948 with undiagnosed failure to thrive and hepatic cirrhosis, was diagnosed in retrospect to have suffered from the same disease. This first case was recently discussed with reference to the presence of advanced cirrhosis of the liver in childhood (Perry).

Since then we have seen 3 cases from different families making a total of 5 patients, of whom 2 are living. The diagnosis of these cases has been established by clinical observation supported by galactose tolerance curves. Paper partition chromatography has shown the presence of galactose in the urine in all cases, and in the last 2 cases the presence of excess amino acids has also been demonstrated in the urine. This latter feature of the disease has recently been described by Holzel, Komrower and Wilson, Robertson and Cusworth, Dent and Flynn.

The reason for the occurrence of severe hepatic cirrhosis in galactose intolerance is obscure. Interest in this aspect of the disease led us to seek a suitable experimental animal. Previously, workers had successfully produced cataracts, but not cirrhosis of the liver, in rats subjected to increased galactose intake (Best and Taylor; Craig and Maddock).

All mammals supply galactose in breast milk which implies that their offspring have an effective mechanism for galactose metabolism. These considerations suggested that the chick might be lacking this and might, therefore, be a suitable experimental animal to investigate the problem. When work had been in progress for some considerable time it was found that Dam had previously observed that a diet containing 54.6% of galactose caused death in chicks.

Technical Methods

Blood glucose was determined by the method of Somogyi (1952), following precipitation of proteins by the method of Somogyi (1945). Blood galactose was determined by the same methods after removal of fermentable reducing substances by incubation with washed baker's yeast. Plasma alpha amino nitrogen was determined by the method of Hamilton and Van Slyke. Histidine determinations were made by the method of Macpherson.

Lethal Effect of Dietary Galactose

Fifty chicks were fed, *ad lib.*, on a pellet diet (Barastoc) and were given galactose (10% w/v., Kerfoot's or B.D.H.) in the drinking water. Deterioration in physical condition, with lethargy and feather drooping, resulted (Figs. 1, 2, 3), and death

Fig. 1. Photograph of 10 weeks chick showing drooping of plumage and lethargic state after 10 % galactose in drinking water for 3 days.

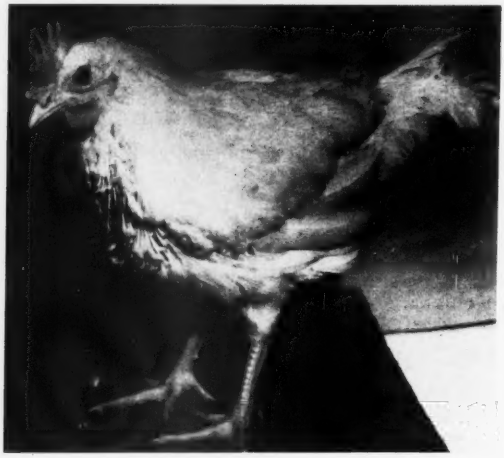

Fig. 2. Photograph of same bird as in Fig. 1, showing normal alert appearance 6 days after removal of galactose from diet.

occurred in all birds before the 8th day. The mean survival time was 4 days. Seventeen chicks given 5 % galactose in their drinking water survived longer, but all died before the 26th day. The mean survival time was 12 days. When the concentration of galactose was reduced to $2\frac{1}{2}$ % some animals survived until the 35th day, but death occurred in all. In a group of 9 chicks the mean survival time was 21 days.

Fig. 3. Photograph of 3 weeks chick on $2\frac{1}{2}$ % galactose since hatching. Taken day before death.

Histological and Histochemical Examination of Chick Tissues

Tissues were removed after death from birds on 10 % galactose and fixed in 4 % formal saline and Masson's fixative. With haematoxylin and eosin staining no abnormality was detected in the pancreas, liver, kidney, cardiac or skeletal muscle.

The livers always showed cells well filled with glycogen, using Best's carmine and periodic acid Schiff stains. This feature led us to investigate the glycogen of several such livers by alkali extraction (boiling for 30 minutes in 30 % KOH), precipitation with 95 % ethanol and hydrolysis with normal sulphuric acid.

Paper chromatography, using butanol/acetic acid/water, 4/1/5 mixture as a solvent and spraying with aniline hydrogen phthalate, showed glucose to be the only carbohydrate present.

General Effect of Dietary Galactose

Chicks on 10 % galactose lost weight progressively until their death, but those on 5 % and $2\frac{1}{2}$ % galactose showed a gain in weight during the experiment. It was much less, however, than the gain shown by control birds on water or equivalent concentrations of glucose.

Galactose was demonstrated in the cloacal contents and in the aqueous humour of birds on all concentrations of galactose. A striking feature shown by chicks on 10 % galactose was the occurrence of epileptiform fits with tonic and clonic phases, followed by a period of flaccidity.

Blood Glucose and Galactose

This observation in animals whose carbohydrate intake had been altered, focussed attention on the level of blood glucose and the possibility of lowered

TABLE 1

Blood glucose and galactose levels in chicks subjected to 10 % galactose in drinking water.

Chick number	Glucose mg per 100 ml	Galactose mg per 100 ml	Chick number	Glucose mg per 100 ml	Galactose mg per 100 ml
1	110	40	16	204	291
2	122	336	17	204	411
3	136	696	18	205	352
4	143	39	19	211	416
5	154	1,003	20	215	74
6	156	16	21	215	160
7	160	392	22	218	133
8	173	296	23	231	144
9	176	688	24	233	928
10	179	64	25	234	507
11	182	48	26	296	> 1,400
12	182	174	27	632	592
13	188	379	28	930	1,735
14	194	672	29	976	1,344
15	196	382			

Blood for galactose estimation was usually taken on the third day.

blood glucose as an explanation of fitting, led us in parallel experiments to examine glucose and galactose levels.

In control birds glucose only was determined, which showed a mean level of 190 mg per 100 ml with a standard deviation of ± 21.

However, glucose and galactose levels in chicks of the same age, having 10 % galactose in their drinking water, showed enormous variations (Table 1). There was no correlation between levels of glucose and galactose and the severity of symptoms. No correlation was noted between glucose levels and the occurrence of fits. Insulin, which reduced blood glucose to low levels, did not initiate fits in chicks taking 10 % w/v. galactose. Galactose levels were also lowered by insulin administration. We have been unable to relate the occurrence of fits in chicks on galactose either to the absolute concentrations of glucose or galactose in the blood, or to their mutual relations.

Investigation of Amino Acids

Examination of cloacal contents for amino acids by paper chromatography showed an increased output in chicks fed galactose. Because of technical difficulty in the collection of urine, the relative contributions made

by the urine and faeces to the amino acid present in the cloacal contents has not as yet been determined, although in humans with galactose intolerance increased amino acid excretion does occur in the urine.

This suggested that the presence of galactose is associated with diminished absorption of amino acids from the renal tubule, and it seemed possible that the same phenomenon might occur in the gut.

The levels of plasma alpha amino nitrogen in normal and galactose fed chicks were determined on the premise that lowered levels might indicate that amino acids were being absorbed from the gut at a lowered rate.

The levels were found to be lower in galactose fed chicks, Table 2. It can be seen from Table 3 that plasma alpha amino nitrogen levels were restored 6 days after galactose had been withdrawn from the diet.

TABLE 2

Comparison of plasma alpha amino nitrogen levels in chicks receiving galactose 10 % w/v. in drinking water and in normal controls.

	Mg alpha amino nitrogen per 100 ml plasma							Mean
Chicks receiving galactose	5.7	5.9	6.1	6.3	6.6	6.7		7.6 ± 1.2
	7.0	7.0	7.0	7.2	7.4			
	7.4	7.7	7.8	8.0	8.0			
	8.4	8.7	8.8	8.8	9.0	9.1	10.1	
Chicks receiving no galactose	6.3	7.7	8.0	8.6	9.8			10.5 ± 2.4
	9.9	10.1	10.2	10.4	10.4			
	10.9	11.1	11.2	13.3	14.9			
	15.0							

TABLE 3

Plasma amino acid levels (mg alpha amino nitrogen per 100 ml) on a group of chicks on 10 % galactose and repeated 6 days after removal of galactose from diet.

Chick number	On 10 % galactose	6 days after galactose stopped
1	5.9	10.0
2	7.0	11.7
3	9.4	12.3
4	6.9	10.3
5	7.3	15.1
6	11.2	16.7
7	8.2	10.7

It has been shown that the transport of amino acids by perfused loops of gut from the rat, and the uptake of amino acids by segments of gut, is a process that requires energy from respiration (Agar, Hird and Sidhu 1953; Agar, Hird and Sidhu 1954). Systems such as these, therefore, seemed suitable to investigate—(a) whether galactose would support the active uptake of an amino acid, and (b) whether galactose interfered with the utilisation of the tissue's endogenous energy sources for uptake.

Methods

Preliminary experiments with transport by isolated loops and uptake by segments of gut suggested that the latter method was more suitable with tissue from the chick.

Chicks, 2–4 weeks old, were starved 24 hours to reduce the content of solids in the gut. With the exception of the following modifications, the tissue was prepared by the method used for the rat (Agar *et al.* 1954). After dissecting away the pancreas the whole of the small intestine, from the crop to the caecum, was slit open and cut into pieces (0.5 cm long) with a scalpel. To eliminate possible variations along the length of gut the tissue was sampled in the following manner: If two experiments were done on the same length of gut, every alternate segment was taken for each experimental system; if three experiments were done on the length of gut, every third segment was taken, and so on. After excess liquid was removed from the segments with filter paper they were weighed and preincubated in Kreb's bicarbonate buffer to which the appropriate sugar and/or 2:4 dinitrophenol were added. This medium was similar to the final incubation medium except that the amino acid was not included. The system was gassed with oxygencontaining 5 % carbon dioxide. The pre-incubation, lasting 10 minutes, served to wash the tissue further and to allow the galactose and dinitrophenol to enter the tissue before incubation in the final system.

The segments were incubated in 10–20 ml of the medium containing L-histidine (5mM). Glucose and galactose were used at a concentration of 0.5 %. Dinitrophenol was used at a concentration of 10^{-3} M. Samples of 0.7 ml were taken at 0, 15, 30, 45 and 75 minutes and the histidine content determined by the method of Macpherson.

Results

The uptake of L-histidine by the tissue was calculated from the change of concentration in the medium. Under similar conditions in the rat, L-histidine is not metabolised. The uptake curve by segments of gut from the chick flattens off just as it does in the rat (Agar *et al.* 1954). It has, therefore, been assumed that the removal of L-histidine from the medium by segments of gut from the chick represents uptake and not metabolism.

Uptake of L-*Histidine*

Effect of 2:4 dinitrophenol.—Dinitrophenol (10^{-3} M) caused a marked reduction in the rate and in the total amount of uptake of L-histidine by the segments (Fig. 4). As dinitrophenol is known to interfere with the supply of useful energy from respiration, it is considered that the latter is involved in the uptake of amino acids, just as in the rat (Agar *et al.* 1953, 1954).

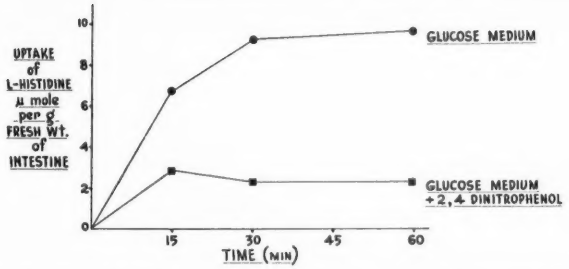

Fig. 4. Graph showing reduction of uptake of the amino acid L-histidine by segments of chick bowel in the presence of 2:4 dinitrophenol. The lower curve shows the effect of 2:4 dinitrophenol which interferes with the supply of useful energy from respiration.

Effect of the Addition of Glucose and Galactose on Uptake

Fig. 5 shows that glucose supports and maintains the uptake of L-histidine over the experimental period. Endogenous energy sources, however, are exhausted after about 30 minutes and the amino acid taken up is then steadily released back into the medium. The curve for galactose clearly shows that this sugar is unable to support the uptake process. It also shows that in its presence the endogenous energy sources are used less effectively.

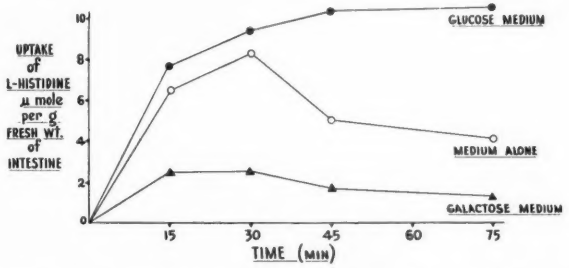

Fig. 5. Graph showing the uptake of L-histidine by segments of chick bowel in the presence of galactose and glucose. The galactose effect simulates that shown by 2:4 dinitrophenol in Fig. 4.

Shedding of Mucosa

There was little, if any, shedding of mucosa by segments incubated in the glucose medium. In the presence of galactose, however, shedding, causing turbidity of the Kreb's buffer system, had already begun during the pre-incubation period.

Microscopic examination of centrifuged deposit showed shed mucosal cells occurring singly and in clumps. Samples taken at 60 minutes and 75 minutes showed many disrupted cells. At the end of the 75-minute period of incubation the tissue had lost up to 46 % of its wet weight (Table 4). The control tissue, without added sugars, had also shed a great deal of mucosa after this time. The onset of shedding, however, is much later than in the presence of galactose. Histological examination of the gut at

TABLE 4

Changes in fresh and dry weights of intestinal segments during incubation in the presence of galactose and glucose.

Expt, No.	Sugar added to incubation medium (0.5 % w/v.)	Initial fresh weight (g)	Final fresh weight (g)	Change in fresh weight (g)	% change in fresh weight	Final dry weight (g)	Percentage dry weight of initial fresh weight
1	Glucose	1.287	1.476	+ 0.189	+ 15	0.245	19
2	,,	1.086	1.203	+ 0.117	+ 10	0.206	19
3	,,	1.610	1.596	− 0.014	− 1	0.271	17
4	,,	3.618	3.718	+ 0.100	+ 3	0.587	16
1	Galactose	1.323	0.748	− 0.575	− 44	0.132	10
2	,,	1.181	0.833	− 0.348	− 30	0.145	12
3	,,	1.453	0.818	− 0.635	− 44	0.142	10
4	,,	3.397	1.833	− 1.564	− 46	0.321	9
5	,,	2.380	1.297	− 1.083	− 46	0.229	10
1	Medium only	1.310	0.778	− 0.532	− 41	0.134	10
2	,, ,,	1.171	0.765	− 0.406	− 35	0.138	12
5	,, ,,	2.301	1.246	− 1.055	− 46	0.216	9

the end of the experiment confirmed the above observations on mucosal shedding (Figs. 6 and 7). The integrity of the mucosa and the process of uptake in vitro, therefore, both seem to be related to metabolic processes.

Fig. 6. Photomicrograph of segment of small intestine of chick submitted to 0.5 % glucose for 75 minutes during uptake experiment. Haematoxylin and eosin × 180.

Fig. 7. Photomicrograph of segment of small intestine of same chick submitted to 0.5% galactose for 75 minutes during uptake experiment. Denudation of villi is clearly seen. Haematoxylin and eosin ×180.

Discussion

Both chicks and humans with galactose intolerance show failure to thrive, disturbance of the central nervous system, galactosaemia and increased excretion of amino acids, after the administration of galactose. These similarities suggest that the chick may be a suitable experimental animal to investigate galactose intolerance.

From our experimental work on the chick it is clear that galactose is unable to supply the necessary energy for uptake of amino acids by the gut. It also seems possible that it interferes with the utilisation of endogenous energy sources. In the latter connexion it is of interest that Schwarz *et al.* found that galactose inhibited the oxygen consumption of red blood cells from patients with galactose intolerance. The results of these workers suggest that a block in the metabolism of galactose-1-phosphate is a biochemical feature of the disease. It seems unlikely, however, that, in the presence of glucose, a missing step in the conversion of galactose to glucose could be a cause of the disease in itself. It seems more likely that galactose and/or galactose-1-phosphate accumulate and act as inhibitors of a step or steps in the metabolism of glucose.

It is probable that uptake by the mucosa is the first step in the absorption of amino acids (Agar *et al.* 1954). The considerable drop in the rate of uptake of an amino acid by the gut of the chick when galactose was added, suggests that the absorption of amino acids may be reduced in the presence

of galactose. The low alpha amino nitrogen in the plasma of chicks fed galactose may, therefore, have its origin in defective absorption by the intestine. Our experiments have been short term ones only, and we have not observed the liver damage which is associated with galactose intolerance. It has been suggested, however, that the origin of the liver damage associated with this disease, may be related to losses of amino acids in the urine (Fox, Fyfe and Mollison). An additional factor in keeping with accepted views on nutritional cirrhosis of the liver may be the inadequate supply of certain amino acids by interference with absorption from the gut.

The evidence obtained so far suggests that galactose and/or galactose-1-phosphate interferes with the supply of useful energy to the tissue cells. Such an interference would undoubtedly lead to a multiplicity of disorders of which reduced absorption, or reabsorption, of amino acids is only one. It would seem that the most profitable approach to the problem would be to identify the inhibitor resulting from the administration of galactose, and to investigate the severity of symptoms produced with varying ratios of galactose and glucose in the diet.

It is hoped that the chick will prove a useful experimental animal with which to investigate further.

Summary

The effect of adding galactose to the diet of chicks has been studied.

Concentrations of 10 %, 5 % and $2\frac{1}{2}$ % w/v. in drinking water were uniformly fatal, the survival time varying inversely with the dose.

During life the birds showed increased blood galactose levels, reduced plasma alpha amino nitrogen levels and were subject to fits.

Failure to thrive, involvement of the central nervous system, galactosaemia and increased galactose excretion are features common to both the human and the experimental disease. These features have been emphasised in support of the chick as an experimental animal for the investigation of galactose intolerance.

It was found in vitro, using segments of chicks' gut, that galactose did not support the uptake of the amino acid L-histidine. It is suggested that if galactose and/or galactose-1-phosphate interfere with the supply of useful energy to tissue cells, this might lead to a multiplicity of disorders of which reduced absorption of amino acids is only one.

Intolerance au galactose. Observations sur un animal de laboratoire.

On a étudié l'effet de l'addition de galactose au régime de poulets. Des concentrations de 10, 5 et 2,5 % dans l'eau de boisson se sont toujours montrées mortelles, la durée de la survie ayant été inversément proportionelle aux concentrations. Durant leur survie, les oiseaux ont montré un accroissement de la galactosémie, une réduction de l'alpha-amino nitrogène et furent sujets à des convulsions. Ralentissement de la croissance, dégénérescence du système nerveux central, galactosémie et augmentation

de l'excrétion du galactose sont des symptomes de la maladie, à la fois, chez l'homme et l'animal de laboratoire. On a déduit de ces faits que le poulet est un animal de choix pour l'expérimentation sur l'intolérance au galactose. On a prouvé, in vitro, en employant des intestins de poulet, que le galactose ne favorise pas la résorption de l'acide aminé, L-histidine. On suggère que, si le galactose ou/et le 1-phosphate de galactose empèchent l'apport d'énergie utile aux cellules, cela peut mener à de nombreux désordres et, parmi ceux-ci, à la diminution de l'absorption des acides aminés.

Galaktoseintoleranz: Beobachtungen an einem Versuchstier.

Die Wirkung des Zusatzes von Galaktose zur Nahrung von Hühnern ist untersucht worden. Konzentrationen von 10, 5 und 2,5 % W/V im Trinkwasser waren gleichformig tödlich, die Überlebensdauer variierte umgekehrt mit der Dosis. Während des Lebens zeigten die Vögel erhöhte Blutgalaktosespiegel, herabgesetzte Alphaaminostrogen-Werte im Plasma und neigten zu Anfällen. Mangelndes Gedeihen, Beeinträchtigung des Zentralnervensystems, Galaktosaemie und erhöhte Galaktoseausscheidung sind Zeichen, die sowohl der menschlichen wie der experimentellen Erkrankung eigen sind. Diese Merkmale konnten mit Hilfe des Huhnes als Versuchstier für die Untersuchungen der Galaktoseintoleranz nachdrücklich betont werden. Es wurde in vitro, indem man Segmente von Hühnerdarm benutzte, gefunden, dass Galaktose nicht die Aufnahme von Aminosäure L-Histidin unterstützt. Es wird angedeutet, dass wenn Galaktose und/oder Galaktose-1-Phosphate störend in die Zufuhr von nützlicher Energie zu den Gewebezellen eingreifen, dies zu einer Vielzahl von Störungen führen kann, wovon die herabgesetzte Absorption von Aminosäure nur eine ist.

Intolerancia a la galactosa. Observaciones experimentales en pollos.

Se agregó galactosa a una dieta suministrada a pollos. Concentraciones de 10, 5 y 2,5 % W/V en el agua fueron uniformemente fatales, variando el tiempo de supervivencia en relación inversa a la dosis. Mientras permanecieron vivas, las aves mostraron niveles altos de galactosemia, bajo alfa amino nitrógeno plasmático y convulsiones. Retardo de adaptación, compromiso del sistema nervioso central, galactosemia y aumento de la excreción de galactosa son hallazgos comunes a enfermos humanos y enfermedad experimental, hecho que muestra que el pollo se adapta bien a la experimentación con esta substancia. En intestinos in-vitro, la galactosa se mostró no contribuir al aprovechamiento de la L-histidina. Es sugerido que si la galactosa y/o galactosa 1 fosfato interfieren el aporte de energía utilizable hacia los tejidos esto puede resultar en una serie de desórdenes de los cuales la reducida absorción de aminoácidos solo sería uno.

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Methemalbuminemia in the Neonatal Period with Special Reference to Hemolytic Disease of the Newborn[1]

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Methemalbumin (ferrihemalbumin), a pigment consisting of oxidized hematin as the prosthetic group and native serum albumin as the protein component, was first described by Fairley & Bromfield (1934) who found the pigment in serum from a patient with "blackwater fever". Subsequently, methemalbumin was found in association with hemoglobinemia, hemoglobinuria and in other hemolytic syndromes characterized by intravascular hemolysis, such as paroxysmal nocturnal hemoglobinuria (cf. Fairley). However, the appearance of methemalbuminemia does not necessarily presuppose a severe hemolytic process since the pigment may also occur in association with severe liver damage and certain drug intoxications (cf. Lemberg & Legge).

Hematin was demonstrated in the cord blood of newborn infants in 1924 by Hasselhorst & Papendiech. Recently, Tuttle (1955) has shown that the hematin which sometimes appears in normal newborn cord blood is bound to albumin, constituting methemalbuminemia. Tuttle also found that there may be a marked elevation of the methemalbumin level in erythroblastotic infants, as had been indicated by Abelson & Boggs from the results of direct spectrophotometric analyses of diluted sera. Although Boggs & Abelson have suggested that the serum hemochromogen level might be used as a guide to replacement transfusion therapy, the clinical significance of methemalbuminemia in the neonatal period remains obscure.

In this study some observations concerning the occurrence of methemalbumin and other heme compounds in the peripheral blood of normal and erythroblastotic babies are reported, together with a discussion of the relationship between the level of these pigments and the severity of the hemolytic process.

[1] Aided by a grant from the Swedish Medical Research Council.

Material and Methods

Ten apparently normal newborn infants and 14 full-term Rh-isoimmunized infants were studied. Clinical data from the isoimmunized infants are given in Table 1.

Venous blood was withdrawn from the internal jugular vein or from the cord with all possible precaution to avoid hemolysis. The blood was allowed to clot for one hour before centrifugation after which the serum was promptly removed and kept in a freezer at −18°C until analysed.

Spectrophotometric absorption studies of serum were performed with the aid of the Beckman Model B spectrophotometer. Serum was employed in dilutions of 1:10–1:20 with physiologic saline. Total hemochromogen levels were determined with benzidine reagent according to the method of Wu, as modified by Bing & Baker (cf. Ham). For the qualitative assay of hematin in serum the Schumm test was applied (cf. Ham). A rough quantitative estimation of the methemalbumin concentration in serum was obtained by the addition of 0.4 ml of saturated ammonium sulphide to 0.3 ml of serum diluted with 3.3 ml of physiologic saline, using the formula:

$$\text{mg per 100 ml methemalbumin} = 2.0\,(\text{O.D. } 555\ \text{m}\mu - \text{O.D. } 570\ \text{m}\mu - 0.004)$$

The ammonium sulphide reagent diluted with saline was used as a blank (cf. Escardó, Karlberg, Stempfel & Zetterström).

Serum bilirubin was determined according to the method of Malloy & Evelyn, as modified by Ducci & Watson.

Paper electrophoretic separation of the serum proteins was carried out with the open-strip method of Durrum. After drying, the strips were stained in 1 per cent bromphenol blue. When the concentration was sufficiently high, the serum hemochromogen was visualized in the unstained strips. To determine the proportion of methemalbumin to hemoglobin, unstained strips were sectioned according to the protein separation which had been obtained from a stained control strip which was run in parallel. The strips were then eluted in 1 ml of the benzidine reagent and 1 ml of 0.6 per cent hydrogen peroxide for one hour, as described by Tuttle. The hemochromogen concentration in each strip section was then determined spectrophotometrically. The heme component migrating with albumin was considered to be methemalbumin (cf. Fairley) and the one migrating with the globulins, hemoglobin. As a control, hemoglobin from one of the erythroblastotic babies was prepared and subjected to electrophoresis as described by Block, Durrum & Zweig.

Table 1

Clinical course, total serum hemochromogen concentrations and serum methemalbumin levels in 14 isoimmunized full-term newborn infants.

	Age	Hemoglobin g/100 ml	Nucleated red cells per c. mm	Serum bilirubin, mg per 100 ml		Serum hemochromogens, mg per 100 ml	
				Direct	Total	Total	Methemalbumin
Case 1							
Progress: No symptoms of disease during neonatal period. No treatment.	Cord	14.2	300	0.2	1.0	15	0
	1 day			0.5	3.5	6	0
	2 days			0.8	5.1	2	0
Case 2							
Progress: No symptoms of disease at birth. Developed intense jaundice rapidly. Exchange transfusion when 18 hours old.	Cord	14.9	1,300		3.7	32	6
	12 hours			1.3	14.8		
	36 ,,			1.3	18.9		
	84 ,,			0.8	16.7		
Case 3							
Progress: Mild symptoms at birth. Developed marked jaundice on the 4th day when there also was vomiting and lethargy.	Cord	12.0	14,000	0.2	1.8	104	16
	24 hours			0.9	8.4	70	28
	2 days			1.8	14.4	68	12
	3 ,,			2.7	18.8	78	6
	4 ,,			1.4	16.2	50	
Case 4							
Progress: Moderate disease. No complications. Exchange transfusion when 4 hours old.	Cord	9.8	320	0.3	0.9	75	30
	4 hours			0.2	1.2		
	5 ,,			*0.2*	*0.7*		
	24 ,,			0.7	3.2		
	2 days				2.8		
Case 5							
Progress: Moderate disease. Slight lethargy on 2nd day when there was marked jaundice. Exch. transfusion 3 hours after birth.	Cord	7.5	20,000	1.1	9.2	21	0
	4 hours			*1.0*	*9.8*		
	17 ,,			1.9	19.3		
Case 6							
Progess: Moderate disease at birth. Developed intense jaundice but no symptoms of brain damage. Two exch. transfusions, 2 hours and 26 hours after birth.	Cord	7.8	11,000	1.0	6.6	25	0
	2 hours			1.4	10.4	8	0
	3 ,,			*0.9*	*4.4*	*20*	*0*
	20 ,,			2.1	17.6	10	0
	24 ,,			1.3	15.6		
	25 ,,			*0.8*	*8.4*		
	2 days			1.8	17.2		
	3 ,,				8		

(Table 1, cont.)

	Age	Hemoglobin g/100 ml	Nucleated red cells per c. mm	Serum bilirubin, mg per 100 ml		Serum hemochromogens, mg per 100 ml	
				Direct	Total	Total	Methemalbumin
Case 7							
Progress: Severe disease.	Cord	7.6	158,000	1.2	6.6	193	9
Uncomplicated course after	3 hours			1.6	10.5	205	15
one exchange transfusion,	4 ,,			*0.8*	*6.8*	*175*	*4*
3 hours after birth.	16 ,,				12.7		
Case 8							
Progress: Severe disease,	Cord	9.9	15,000	0.8	7.0	19	1
developed intense jaundice	4 hours			1.7	12.4	9	6
but no symptoms of brain	5 ,,			*0.8*	*7.4*	*12*	
damage. Exchange trans-	26 ,,			2.1	20.6	8	7
fused twice, 4 hours and	27 ,,			*1.1*	*13.2*	*1*	*0*
26 hours after birth.	46 ,,				18.0	4	
	70 ,,			1.8	20.9		
	92 ,,			0.8	13.4		
Case 9							
Progress: Severe disease.	Cord	5.0	60,000	0.8	2.8		150
Developed intense jaun-	4 hours			1.8	6.4		
dice and definite though	5 ,,			*1.2*	*5.7*		
mild symptoms of kern-	24 ,,				19.4		
icterus. Two exchange	48 ,,			6.9	18.0		64
transfusions, 4 hours and	49 ,,			*3.8*	*9.0*		*30*
48 hours after birth.	3 days			4.1	11.8		26
Slight obstructive type of	4 ,,			4.4	12.0		14
jaundice.	5 ,,			3.8	8.2		4
Case 10							
Progress: Severe disease	Cord	6.8	27,000	2.1	6.0	216	38
complicated by obstructive	2 hours			2.9	9.4	342	54
jaundice. No symptoms of	3 ,,			*1.8*	*5.0*	*94*	*40*
brain damage. Exchange	37 ,,			9.4	24.2		
transfusions, when 2 and	43 ,,			10.8	25.4	90	36
43 hours old.	44 ,,			*5.9*	*13.2*	*53*	*18*
	4 days			7.4	15.5		
Case 11							
Progress: Severe disease,	Cord	9.9	54,000				
complicated by obstructive	2 hours			6.3	11.8	284	188
type of jaundice. Symp-	3 ,,			*3.2*	*6.6*	*173*	*82*
toms of circulatory failure	33 ,,			9.3	20.2		
first day of life. No signs	57 ,,			7.9	20.0		
of brain damage. Two	81 ,,			7.4	14.4	70	58
exch. transfusions, 2 and	82 ,,			*3.3*	*5.8*	*54*	*46*
21 hours after birth.	4 days			5.9	10.4	34	

(Table 1, cont.)

	Age	Hemoglobin g/100 ml	Nucleated red cells per c. mm	Serum bilirubin, mg per 100 ml		Serum hemochromogens, mg per 100 ml	
				Direct	Total	Total	Methemalbumin
Case 12							
Progress: Severe disease complicated by obstructive type of jaundice.	Cord	11.0	144,000	5.4	10.1	132	72
Case 13							
Progress: Edematous infant who expired from circulatory failure at an age of 2 hours.	Cord	6.1	50,000	8.8	12.6	117	66
Case 14							
Stillborn hydropic infant.	Cord	3.7	95,000	0.5	2.3	153	105

(Italics indicate values obtained immediately after exchange transfusions.)

Results

In full-term infants which were apparently normal, the Schumm hematin test was positive in the cord blood of 3 out of 10 cases. However, in none of the samples giving a positive test was the methemalbumin concentration high enough to give a significant absorption peak between 620 and 625 mμ (the region in which the alpha band of methemalbumin characteristically appears (Fairley)). Quantitative measurements of the total hemochromogen level in these sera showed values varying between 5 and 25 mg per 100 ml,

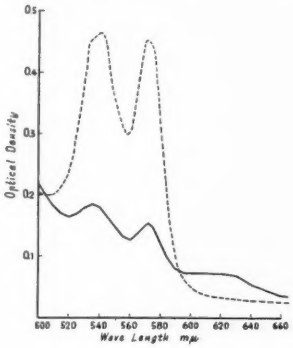

Chart 1. Spectrophotometric absorption curves of cord serum diluted 1:10 with 0.9 per cent saline (lower curve) and a solution of purified hemoglobin (upper curve) from a stillborn hydropic isoimmunized infant (Case 14, Table 1). In the spectrum of the hemoglobin solution there is one peak at 540 mμ, and another at 570 mμ. In the serum spectrum there are two peaks corresponding to those of hemoglobin but also a third peak at about 620 mμ, corresponding to the alpha-band of methemalbumin.

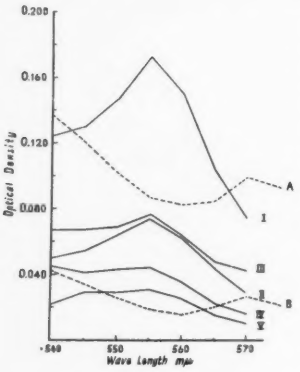

Chart 2. Spectrophotometric absorption curves of serum diluted 1:13 with 0.9 per cent saline (dotted lines) and after the addition of the Schumm reagent to dilute serial serum samples (unbroken lines) from an infant with hemolytic disease of the newborn (Case 11, Table). The chart demonstrates the successive decrease in the serum methemalbumin level during the period of observation. Note the peak at 570 mμ in the absorption curves from the serum samples. After the addition of the Schumm reagent a hemochromogen with a sharp peak at 555 mμ is formed from methemalbumin. *A*, from serum before the first exchange. *B*, from serum after the first exchange transfusion. I–V represent curves obtained after the addition of Schumm's reagent. I, before the first exchange transfusion, 2 hours after birth. II, after first exchange transfusion, 3 hours after birth. III, before second exchange transfusion, 81 hours after birth. IV, after second exchange transfusion, 82 hours after birth. V, at an age of 4 days.

which is within the approximate range of normal in adults (Crosby). On the second day of life the Schumm test was negative in all infants studied and methemalbumin was no longer detected in the serum.

Infants with hemolytic disease of the newborn: Chart 1 demonstrates the spectrum of cord serum diluted 1:10 compared with the spectrum of a pure hemoglobin solution prepared from red cells from a hydropic stillborn infant (Case 14, Table 1). In the wave-length region studied, hemoglobin has a broad peak at 540 mμ and a narrower peak at 570 mμ. In the serum sample there was another peak at about 620 mμ, corresponding to the alpha band of methemalbumin. That hematin was present in this serum sample was demonstrated by a positive Schumm test. After electrophoretic separation of the serum proteins, 70 per cent of the hemochromogens were localized in the albumin fraction. The remaining heme compounds were found in the globulin fractions, especially beta-globulin, demonstrating that in this case methemalbumin accounted for more than two-thirds of the total hemochromogen content in the cord serum. The absorption curve obtained seems to indicate that the remaining fraction was hemoglobin.

Serum hematin levels during the course of the disease as measured by the Schumm test in Case 11 are shown in Chart 2. After addition of the Schumm reagent to a diluted serum sample covered with a thin layer of ether, a hemochromogen with a sharp peak between 555 and 560 mμ was formed. The chart also illustrates the efficiency of exchange transfusion in lowering the methemalbumin level.

The clinical significance of high concentrations of methemalbumin in the cord blood and during the first days of life can be evaluated to some extent from the data given in Table 1. Although a marked elevation of this level in cord serum was found only in association with severe hemolytic disease,

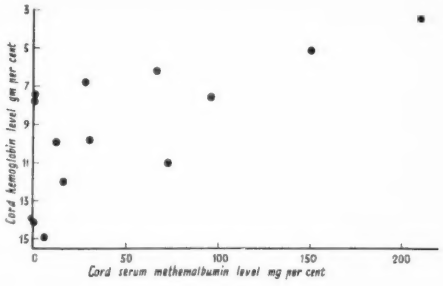

Chart 3. Scattergram of cord serum methemalbumin levels from 13 cases of hemolytic disease of the newborn plotted against the corresponding hemoglobin values. Although there is a trend, no absolute correlation is found.

it is quite clear that there was no absolute correlation between the severity of the disease and the concentration of this pigment. However, in cases which developed an obstructive type jaundice there was a consistently high serum concentration of methemalbumin. The course of the disease cannot be judged from this level, and some of the infants who had mild symptoms at birth but developed intense jaundice requiring repeated exchange transfusions had little or no methemalbumin in the cord blood (Cases 6 and 8). As is demonstrated in Case 14, a stillborn hydropic infant with a very high methemalbumin concentration, there is also no uniform relationship between the indirect bilirubin and methemalbumin levels.

According to the data given, the production and accumulation of methemalbumin in fetal serum seems to be related to the rate and duration of hemolysis and to the state of liver function.

Although there is a trend, there is no direct correlation between the hemoglobin and methemalbumin concentration in cord blood, as is shown in Chart 3. Methemalbumin may be absent even in cases with very low hemoglobin values. However, when a low hemoglobin level was associated with a high nucleated red cell count, the concentration of methemalbumin was always found to be high. This finding would indicate that a short period of active hemolysis immediately antepartum is not sufficient to cause the formation and subsequent accumulation of this heme compound.

The proportion of free hemoglobin to methemalbumin in the cord serum varied in different cases. Part of the extracorpuscular hemoglobin in the circulating plasma is transformed to methemalbumin which is metabolized within 20 to 26 hours in the presence of normal hepatic function (cf. Fairley). With less adequate liver function the pigment is metabolized at a slower rate. Therefore, the difference observed may be due to individual variations in both intensity and duration of the hemolytic process in addition to variations in the state of prenatal hepatic function. In patients with a high rate of hemolysis which is of short duration during the terminal phases of fetal

life, hemoglobin may be expected to be the predominant heme compound in the cord serum. On the other hand, in infants with long-standing fetal hemolytic disease there may be a progressive accumulation of methemalbumin which may be more pronounced in the presence of liver damage. The possible significance of placental function in regard to this pigment is unknown. A postnatal transformation of hemoglobin to methemalbumin is illustrated in Cases 3 and 5, where there was a relatively high cord serum hemoglobin concentration and a subsequent increase in serum methemalbumin during the first few hours of life.

Serial determinations of the total hemochromogen and methemalbumin levels during the neonatal period (Table 1) show that there is usually a marked fall in heme concentration after the first exchange transfusion and a progressive decrease thereafter. However, detectable amounts of methemalbumin may be found in the serum four to five days after birth in erythroblastosis.

Comment

The observations reported here are in agreement with those of Tuttle and show that methemalbumin may appear as a constituent of cord serum in the normal newborn, though the concentration of this heme compound is extremely low and disappears from the circulation in detectable amounts within the first day of life.

The occurrence of methemalbumin in the cord serum of the normal newborn would indicate that some intravascular hemolysis may take place, even in an uncomplicated fetal existence. With the exception of certain pathologic conditions, red cells destruction is thought to take place in the spleen or other reticuloendothelial tissues in postnatal life. The cause of fetal intravascular hemolysis is obscure, but such factors as intense extramedullary hematopoiesis (cf. Langley) and short life span of fetal erythrocytes (Hollingsworth) may be contributory. Immaturity of the reticuloendothelial system might then be responsible for the slow metabolism of hemoglobin, with a consequent accumulation of methemalbumin.

In hemolytic disease of the newborn, the methemalbumin level was found to be extremely high in most cases with such clinical and hematologic findings as to suggest an intense fetal hemolytic process, and in addition to a high methemalbumin level, there was usually an elevation in serum hemoglobin concentration.

It seems reasonable to assume that methemalbumin often appears in high concentration in hemolytic disease of the newborn, though individual variations in concentration must be extreme. The highest values were

observed in infants with signs of severe hemolytic disease at birth, while in some infants who developed intense jaundice requiring exchange transfusion, the Schumm test for methemalbumin was negative. These findings would indicate that determinations of the methemalbumin concentration cannot be used as a guide to exchange therapy. Furthermore, when there is a marked elevation in methemalbumin there are always other observations which would more clearly point out the necessity of immediate treatment.

Whether or not a high methemalbumin level is innocuous in the fetus or neonate cannot be established from the findings reported here. Although Anderson, Morrison & Williams have demonstrated renal lesions after the intravenous injection of alkaline hematin in dogs, there are no studies which have established hematin toxicity in man. That heme pigments as well as direct and indirect bilirubin can cross the blood-cerebrospinal fluid barrier in the neonatal period has been shown earlier (Stempfel & Zetterström). It follows, therefore, that the methemalbumin concentration in the spinal fluid may be relatively high when that pigment is elevated in the serum. Whether or not the pigment might have a direct toxic effect is unknown, but there is some indication that the compound may cause intracranial hypertension through an over-production of cerebrospinal fluid when it is present in high concentration (Escardó *et al.*). Tuttle has suggested that a high methemalbumin level might interfere with the formation of the bilirubin-albumin complex and in this way predispose the neonatal brain to the toxic effects of free bilirubin.

Summary

Methemalbumin was demonstrated in the cord serum from 3 out of 10 apparently normal newborn infants. This heme pigment which appeared in low concentration disappeared from the peripheral blood during the first day of life.

In infants with hemolytic disease of the newborn, the methemalbumin level was found to be elevated in those cases which exhibited features of a severe hemolytic process *in utero*. A long-standing and intense hemolytic process in addition to hepatic dysfunction was found to be a predisposing factor to the accumulation of methemalbumin in the plasma. In most cases with methemalbuminemia there was a marked elevation of the serum hemoglobin concentration, indicating preceding intravascular hemolysis. In isoimmunized infants with a high level of cord serum hemoglobin there was an increase in the concentration of methemalbumin during the first few hours after birth. Methemalbumin disappeared spontaneously from the serum at a slow rate but, of course, was removed rapidly during exchange transfusion.

The clinical significance of methemalbumin in hemolytic disease of the newborn is briefly discussed. It is concluded that the concentration of this pigment in cord serum cannot be used as a guide to exchange transfusion therapy.

Méthémalbuminémie durant la période néonatale ainsi que ses rapports avec la maladie hémolytique du nouveau-né.

La *méthémalbumine* a été trouvée dans le sérum du sang ombilical chez trois enfants dans un groupe de dix nouveaux-nés apparemment normaux. Ce pigment hématique ne fut présent qu'en faible concentration et disparut du sang périphérique durant le premier jour de la vie. Chez les enfants atteints de la maladie hémolytique du nouveau-né, la concentration en méthémalbumine fut trouvée élevée dans les cas qui montraient les caractéristiques d'un processus sévère d'hemolyse in utero. Une atteinte hémolytique intense et de longue durée, liée à un trouble de la fonction hépatique, s'est montrée un facteur prédisposant à l'accumulation de méthémalbumine dans le plasma. Dans la plupart des cas avec méthémalbuminémie, il existait une augmentation sensible de la concentration de l'hémoglobine dans le sérum, signe d'une hémolyse intravasculaire antérieure. Chez les enfants isoimmunisés, présentants une forte concentration d'hémoglobine dans le sérum du cordon, on a trouvé une augmentation de la méthémalbumine durant les toutes premières heures après la naissance. Spontanément la méthémalbumine disparait lentement du sérum, mais est, évidemment, évacuée rapidement par l'exosanguinotransfusion. La signification clinique de la méthémalbumine dans la maladie hémolytique du nouveau-né est discutée brièvement. La conclusion en a été que l'on ne pouvait se servir de la concentration de ce pigment dans le sérum du cordon ombilical comme d'un critère pour décider l'exosanguinotransfusion.

Methämalbuminämie in der Neugeburtsperiode mit besonderer Berücksichtigung der hämolytischen Erkrankung des Neugeborenen.

Methämalbumin wurde im Nabelschnurserum bei 3 von 10 anscheinend normalen Neugeborenen nachgewiesen. Dieses Blutpigment, das in niederen Konzentrationen erschien, verschwand während der ersten Lebenstage aus dem peripheren Blut. Bei Kindern mit hämolytischen Erkrankungen der Neugeburtsperiode wurde der Methämalbuminspiegel in solchen Fällen erhöht befunden, wo Merkmale eines schweren hämolytischen Prozesses in utero vorlagen. Ein langwieriger und intensiver hämolytischer Prozess mit Leberdysfunktion pflegte ein prädisponierender Faktor für die Anhäufung von Methämalbumin im Plasma zu sein. In den meisten Fällen mit Methämalbuminämie bestand eine ausgeprägte Erhöhung der Serumhämoglobinkonzentration, die auf eine vorausgegangene intravaskuläre Hämolyse hinweist. Bei isoimmunisierten Kindern mit einem hohen Spiegel des Nabelschnurhämoglobins bestand während ein paar Stunden nach der Geburt eine Erhöhung der Methämalbuminkonzentration. Methämalbumin verschwand spontan langsam aus dem Serum, wurde aber natürlich bei Austauschtransfusion schnell entfernt. Die klinische Bedeutung von Methämalbumin bei hämolytischen Erkrankungen Neugeborener wird kurz diskutiert. Es wird der Schluss gezogen, dass die Konzentration dieses Pigments im Nabelschnurserum nicht als Indikator zur Austauschtransfusion dienen kann.

Metahemalbuminemia en el período neonatal y su relación con la enfermedad hemolítica del recién nacido.

Tres entre un grupo de 10 recién nacidos aparentemente normales presentaron metahemalbuminemia en la sangre del cordón. Dicho pigmento cuya concentración fue baja, desapareció del torrente circulatorio en el curso del primer dia de vida. Del grupo de recién nacidos afectos de enfermedad hemolítica, aquellos presentando signos de

severa hemólisis in-utero tuvieron niveles altos de metahemalbúmina. Un proceso hemolítico de larga duración sumado a disfunción hepática mostraron ser factores predisponentes a la acumulación de este pigmento. En la mayoría de los casos hubo también una elevación de la hemoglobina plasmática sugiriendo una hemólisis intravascular anterior. El nivel de metahemalbúmina fué en aumento durante las primeras horas de vida para luego comenzar a decrecer lentamente; la exanguinotransfusión mostró eficacia en su total eliminación. Se discute brevemente la significación clínica de metahemalbuminemia en la enfermedad hemolítica del recién nacido concluyéndose que los niveles de dicho pigmento en la sangre del cordón no pueden ser usados como guía para proceder a la terapéutica de recambio sanguíneo.

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From the Pediatric Clinic, Karolinska Sjukhuset, Stockholm
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Unilateral Clubbing of the Fingers in a Child with Obstruction of the Subclavian Artery

by GUNVOR SVARTZ-MALMBERG

Unilateral clubbing of the fingers is a relatively rare condition. Rodgers tabulates 29 published cases, most of which occurred with aneurysms in the upper limb arteries. In 5 cases, however, no aneurysm could be demonstrated; in one of these patients the clubbing was considered to be due to dislocation of the shoulder, in another to carcinoma of the right upper lobe bronchus, in two to phlebectasias, and in the remaining one to injury of the axillary region. In 1955, Dorney *et al.* described a case of unilateral clubbing of the fingers due to absence of the aortic arch. In this case clubbing and cyanosis were noted not only in one hand but also in both feet.

In his monograph *The Digital Circulation*, Mendlowitz has devoted one chapter to the problem of clubbing. He is of the opinion that "all forms of clubbing may eventually be found to be caused by local oversupply of blood brought about by various mechanisms acting singly or in combination". Mendlowitz does not believe that anoxemia plays any role in the development of clubbing, as has been supposed by earlier authors (e.g. Mauer, Taussig).

In this article an account is given of a case of unilateral clubbing with obstruction of the subclavian artery of the same side.

Case Report

A girl, M. Å., born on Febr. 26, 1949.

No family history of the disease in question. Development normal. Healthy until Febr. 1953, when she fell ill with swelling and tenderness in the right knee-joint. On admission to the Children's department, Norrköping: faint systolic murmur over the heart, SR 35 mm, antistreptolysin titer normal. No abnormality of the fingers noticed. After treatment with penicillin all symptoms disappeared. May 1953: pains in hip-joints and wrists. Jan. 1954: readmitted because of pains and swelling of the wrists and the ankles (SR 71 mm, antistreptolysin titer normal, treated with ACTH and penicillin with good effect). During the next year prophylactic treatment with penicillin

twice a month. No symptoms until March 1955, when readmitted because of pains and aches in the fingertips of the left hand and in the left shoulder and elbow. No swelling of the joints, but swelling of the painful fingertips was observed. SR 28 mm, antistreptolysin titer normal. Again penicillin treatment with good effect, but only for a week, after which she was once more admitted. Clubbing of the fingers of the left hand was then observed. In the left arm the radial pulse could not be felt and the blood pressure was unobtainable. In the left axilla a spindle-shaped, indolent thickening of the vascular stem was felt. The enlarged part of the vessel, 4 cm long and thickest at its proximal end, was not attached to surrounding tissues.

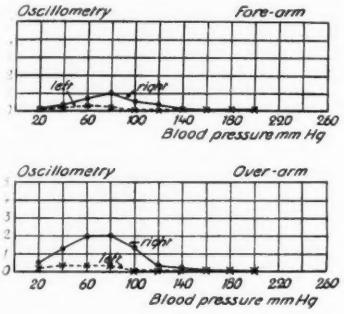

Fig. 1. Oscillometry of the arms.

Referred to the Pediatric Clinic, Karolinska Sjukhuset, for special investigations: On admission on April 26th, 1955 her general condition was good and no swelling of the joints was demonstrable. Nor did she complain of any articular pains. Afebrile. Systolic murmur over the whole heart area (punctum maximum in I:3 sin.). ECG and Wilson essentially normal. Left arm pulseless and blood pressure unobtainable. Blood pressure in right arm: 110/80 mm Hg, in both legs: 115/75 mm Hg. Left brachial artery pulseless and rather thickened. No difference between the circumferences of the two arms. The fingers of the left hand were clubbed, whereas the fingers of the right hand and the toes were of normal size and shape. SR 46 mm, antistreptolysin titer normal.

Special investigations: Radiography of heart and lungs and of the humeroscapular joints were normal. Oscillometry (Fig. 1) showed obturation of the left brachial artery.

Arteriography (Dr. C. O. Ovenfors): According to Seldinger's method a polyethylenic catheter was inserted percutaneously in to the right femoral artery with its tip in the aortic arch. To avoid cerebral complications the concentration of the dye (Umbradil Astra) was kept as low as 35 %. The density of the dye in the vessels therefore became rather low. The great vessels of the neck were well visualized and appeared normal. The left subclavian artery was very thin already at its origin, then successively grew thinner and could be followed only about 9 cm in the distal direction (Fig. 2*a*). A rather extensive ramification of arteries, like that in a collateral circulation, was visualized in the shoulder region (Fig. 2*b*). The roentgenologic investigation thus showed a narrowing of the subclavian artery of obscure etiology.

Surgical exploration (Dr. T. Hierton, the Norrbacka Institute). A 5 cm long incision was made in the left overarm along the margin of the biceps muscle. Two brachial veins were identified and between them a thin artery, 2 mm in diameter.

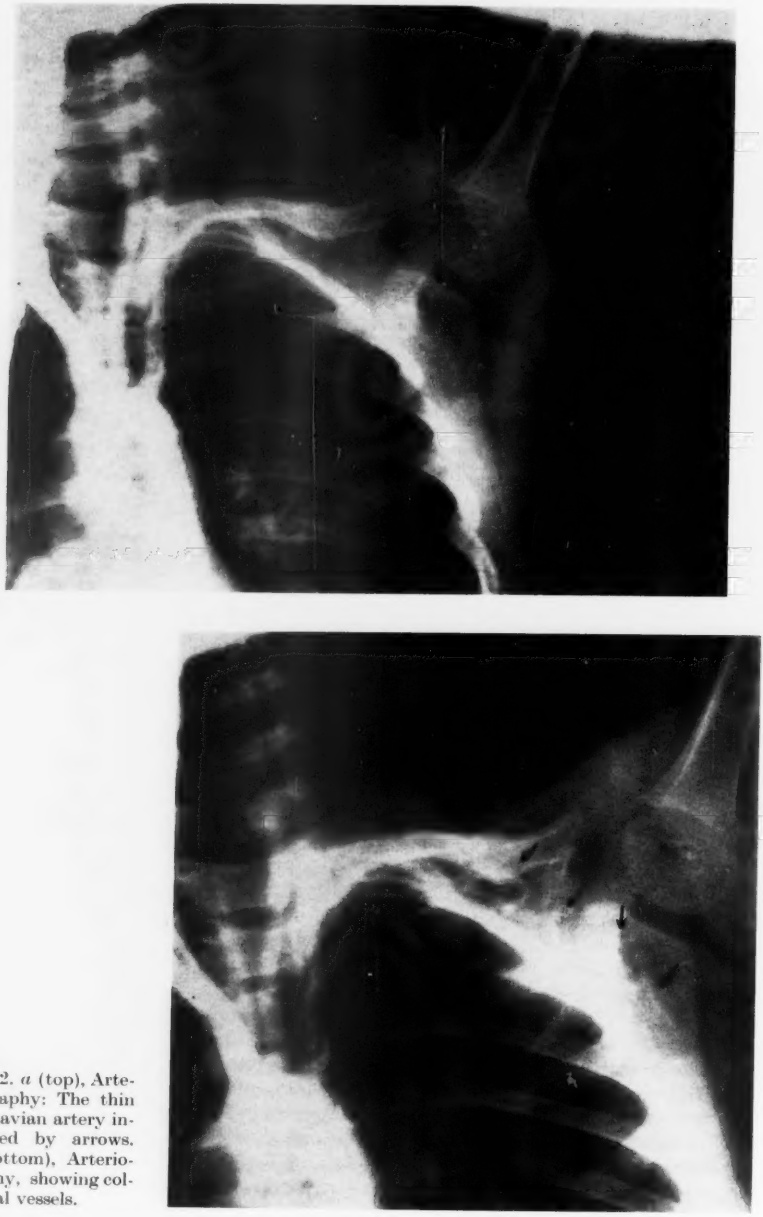

Fig. 2. *a* (top), Arteriography: The thin subclavian artery indicated by arrows. *b* (bottom), Arteriography, showing collateral vessels.

There were no signs of inflammation and it was believed that the subclavian artery was congenitally underdeveloped. A reconstruction of the vessel was considered impossible.

The child was reinvestigated in July–August 1955. The fingers of the left hand were clubbed and no pulses were felt in the left axilla and in the left arm. The clubbing appeared, however, considerably reduced since the previous examination. The thickening of the vascular stem in the left axilla had almost disappeared. The carotid pulses were felt bilaterally and there was no vascular murmur either in the axilla or in the supraclavicular fossa over the origin of the artery. There was no significant difference in length between the left arm and the right one, or between the fingers of the left hand and the fingers of the right one. SR 58 mm. No L.E.-cells found. Agglutination of sensitized sheep cells negative. No eosinophilia. Antistreptolysin titer normal. Electrophoresis normal.

Discussion

It has earlier been assumed that anoxemia in the peripheral tissues might be an essential factor in the development of clubbing. According to this opinion an obstruction of a limb artery would be a highly probable cause of clubbing. However, most cases of unilateral clubbing are due to arterial aneurysms, and Mendlowitz is of the opinion that, on the contrary, *hyper*oxia and *hyper*nutrition are the most important factors in the development of clubbing. In many conditions in which clubbing occurs, an increased blood flow is present, but without a proportionate increase in the systemic demand. Thus an increase in the blood flow to a tissue not demanding more than the normal flow would cause hypernutrition and thence clubbing. This mechanism seems to explain the clubbing of *hypertrophic* osteoarthropathy caused by chronic heart and lung diseases. In the cases of clubbing due to aneurysm in the subclavian artery, a greater quantity of blood than required may reach the peripheral tissue through the dilated vessel. Mendlowitz has also experimentally shown increased blood flow and increased blood pressure in the fingers in such cases. An injury or a tumour may, in damaging the vasomotor nerves, produce a vasodilatation.

But in the case in question here, with an obstruction of the blood flow, an oversupply to the finger tissues would seem rather improbable. It has, however, been experimentally demonstrated (Edholm *et al.*) that an arterial obstruction in which the blood pressure is unobtainable with auscultatory methods, does not necessarily cause a decreased blood flow to the peripheral tissues. In measuring the blood pressure intra-arterially in individuals with unilateral arterial obstruction, it was found that the blood *flow* is often the same in the affected limb as in the healthy one, and that in the former it may even exceed the flow in the healthy one because of the development of collaterals or changes in the vascular tonus.

Thus the occurrence of clubbing in arterial obstruction would be theoreti-

cally possible, but in reviewing the literature it is established that cases showing the combination of pulselessness and clubbing are in reality extremely rare. One such case with syphilitic aneurysm of the aorta has been described by Crawford.

At the surgical exploration in May 1955 the arterial obstruction in the present case was considered to be congenital. Grishman *et al.* describe a case considered to be a congenital arterial anomaly: pulselessness in the left arm, unobtainable blood pressure, but the peripheral parts of the arm were warm and showed no signs of atrophy; angiocardiography showed a normal aorta, but no subclavian artery. Nothing, however, is mentioned about clubbing in this case.

In the case here described the clubbing had obviously decreased at the last examination, and therefore the possibility of an acquired affection, most probably an inflammatory process, must be discussed. The disappearance of the thickening of the vascular stem may also speak in favour of such a process. The surgical exploration was performed distally to this thickening and a thin artery was found. Its thin calibre may have been due to a decrease in the pulse pressure brought about by a proximally located narrowing process.

So far it is impossible to determine with certainty the character of the inflammatory process probably existing in this case. In arteritis the resulting symptoms usually are trophic disturbances, pareses and pains, thus quite different from the symptoms in diseases where clubbing is a common finding. A thorough survey of the arteritides is made by Ross & McKusick. Their cases, however, showed symptoms from at least *two* great vessels from the aortic arch, one of which always was a carotid artery. Pulselessness may be caused by syphilis and by arteriosclerosis, but also by other arteritides, mostly of unknown etiology. To this group belong thrombangitis obliterans periarteritis nodosa, temporal arteritis and young female arteritis.

The affection in our case exhibits some resemblance to temporal arteritis since it showed signs of a localized enlargement of the vessel. Temporal arteritis, however, occurs at an advanced age, but may be connected with joint symptoms (Jennings, cit. Ross & McKusick). Young female arteritis, also called Takayashu's disease or pulseless disease, is a panarteritis of unknown etiology characterized by symptoms originating in the carotid region, such as syncope and visual disturbances as well as blindness, and from the upper limb with pains and pulselessness. This disease, however, has never been described in a child and most frequently occurs in the fertile age (Ask-Upmark). In one patient (Ross & McKusick) a direct correlation to a polyarthritis seemed probable. Clubbing, however, has never been mentioned in the cases of pulseless disease.

In the present case it is impossible to determine the character of the vascular affection. The observed changes of the findings render an acquired process probable, and there is also a possibility that this process is connected with the patient's recidivating joint affection. The further development of the disease may give a definite answer. Although the etiology of the disease is obscure, it may be assumed that the clubbing in this case was caused by the alterations in the blood supply brought about by the vascular obstruction.

Summary

Report of a case of unilateral clubbing, associated with an obstruction of the homolateral subclavian artery. The obstruction was probably of inflammatory origin. Different opinions concerning the etiology of clubbing and various causes of obstruction of the great arteries are shortly reviewed.

Hippocratisme digital unilatéral chez un enfant porteur d'une obstruction de l'artère sous-clavière.

Observation d'un cas d'hippocratisme digital unilatéral où a pu être mise en évidence une obstruction de l'artère sous-clavière du même côté. Cette sténose artérielle fut considérée comme d'origine artéritique. Les diverses théories concernant les causes des hippocratismes et celles des sténoses des gros troncs artériels sont rapidement passés en revue.

Unilaterale Trommelschlägelfinger bei einem Kind mit Obstruktion der Arteria subclavia.

Bericht eines Falles von einseitigen Trommelschlägelfingern, bei dem eine Obstruktion der gleichseitigen Arteria subclavia demonstriert werden konnte. Die Obstruktion wurde als arteriitisch bedingt angesehen. Es wird ein kurzer Überblick über die verschiedenen Anschauungen hinsichtlich der Ätiologie von Trommelschlägelfingern und der verschiedenen Ursachen von Obstruktion der grossen Arterien gegeben.

Dedos hipocráticos unilaterales en un niño con obstrucción de la arteria subclavia.

Un caso con obstrucción, de origen arterítico, de la arteria subclavia, presentó dedos en palillo de tambor en la mano homolateral. Se revisan brevemente diferentes teorías y opiniones sobre factores etiológicos de los dedos hipocráticos y causas de obstrucción de grandes arterias.

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Addendum

On Dec. 29 1955, the patient was again admitted to the Children's De partment, Norrköping. She then complained of pains and aches in th fingers of the *right* hand and it was observed that, now for the first time also the right arm was pulseless. Femoral and popliteal pulses were norma bilaterally. After treatment with ACTH a faint radial pulse could be felt on the right side, but after withdrawal of ACTH it again disappeared. In the left, first affected, arm the pulse has nerver returned.

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From the Pediatric Clinic, Karolinska Sjukhuset, Stockholm

Transient Hemoglobinemia Associated with Hemoglobinuria and Methemalbuminemia in the Neonatal Period

by F. E. ESCARDÓ, P. KARLBERG, R. STEMPFEL[1] AND R. ZETTERSTRÖM

Hemoglobinemia with hemoglobinuria and the subsequent formation of methemalbumin may occur in hemolytic disorders in which intravascular hemolysis takes place, such as "blackwater fever" (Fairley) and paroxysmal nocturnal hemoglobinuria (Crosby, Ham). In the neonatal period and in early infancy, hemoglobinuria seems to be extremely rare but is described in association with sepsis in which an intense hemolytic process and severe jaundice may occur; a syndrome known as Winkel's disease (cf. Polayes & Kramer).

In this report a newborn infant who developed transient hemoglobinuria of unknown etiology, without other hematologic findings suggesting hemolytic disease, will be described. The condition was further characterized by high concentrations of methemalbumin in both the serum and cerebrospinal fluid. Since the methemalbuminemia persisted for several weeks after the disappearance of hemoglobinemia, it was possible to study the metabolism of this pigment. The question of methemalbumin toxicity will also be discussed on the basis of the clinical features in the patient described.

Case Report

The patient, J. P., a 9-day-old male infant, was admitted to the Pediatric Clinic, Karolinska Sjukhuset, because of fever, vomiting, lethargy and symptoms suggestive of brain damage.

This was the first child of healthy parents and the pregnancy was said to have been uncomplicated, though delivery was by low forceps extraction because of questionable neonatal asphyxia. The infant appeared quite normal at birth with a weight of 3940 g. Respiration was established immediately and there was no cyanosis. The first 5 days of life were uncomplicated except for a rather large cephalhematoma.

On the sixth day the child developed a mild temperature elevation (38° C) which was considered to be secondary to dehydration in the absence of other symptoms, but on the following day he began to vomit and became slightly lethargic. On the morning

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of the seventh day the edge of the damp part of the diaper was noted to be stained red. The head circumference which was 37 cm at birth had increased to 39 cm. On the ninth day of life, the vomiting was accentuated and the low-grade fever persisted. At that time the urine became intensely red and the skin developed a pronounced dark bronze coloration.

On admission, physical examination revealed a moderately ill 9-day-old infant who was slightly dehydrated and whose weight was 3650 g. There was a moderately large parietal cephalhematoma. Obvious signs of intracranial hypertension were present with bulging fontanels and separation of the sutures (15 to 20 mm). The eyes appeared sunken. The neck was supple. Muscle tone and grasping and sucking reflexes were normal. The Moro reflex was diminished. There was no unusual irritability and the cry was full. The skin was dark bronze in color and seemed to be somewhat cyanotic, the cyanosis increasing to some extent on crying. No symptoms of respiratory distress were present. There was no cardiac enlargement and the heart sounds were of good quality. There was no hepatosplenomegaly. X-rays of the chest and abdomen revealed no abnormalities.

Laboratory findings.—Hemoglobin 17.2 g per 100 ml, RBC 4.7 per mm^3, WBC 14,000 per mm^3, with normal differential. Reticulocyte count 1.3 %. No coagulation dysfunction was observed. Serum indirect bilirubin 1.6 mg per 100 ml, with no measurable direct-reacting pigment. NPN 53 mg per 100 ml. The serum was dark brown in color and contained heme pigments in high concentration (see below).

The urine was dark red in color and on standing a heavy brown sediment formed which was thought to be composed of heme pigment crystals. This urine contained protein and there were numerous RBC, WBC and casts in the sediment. Spectrophotometric examination revealed a typical oxyhemoglobin spectrum (see below). No urinary porphyrins were detected. After treatment with chloramphenicol over a 36-hour period, a urine culture performed on the second hospital day was sterile.

A lumbar puncture was performed on admission: pressure was found to be about 150 mm H_2O and the fluid had a marked brownish coloration. Protein content was within the normal range and there was no pleocytosis. Cerebrospinal fluid cultures revealed no growth.

The infant's blood was $ARh(-)$, and that of the mother $A_2Rh(-)$. The infant's direct Coombs' test was negative and no irregular agglutinins were present in the mother's serum.

Repeated paper electrophoretic analyses of the serum proteins (open-strip method of Durrum) revealed no abnormalities. A normal decay in gamma-globulin concentration was noted throughout the period of observation.

Treatment and course.—The heme pigment causing the discoloration of the serum and cerebrospinal fluid was found to be methemalbumin (see below). Although there was no evidence that this child had sepsis, he was treated, empirically, with chloramphenicol for 6 days. On admission, intravenous fluid therapy was instituted to correct the mild dehydration and maintain a high urinary output in an effort to avoid possible renal damage from the massive pigment excretion.

The body temperature returned to normal levels on the second hospital day and remained within this range throughout the admission. Vomiting persisted for one week but subsided as the signs of increased intracranial pressure disappeared. Head circumference decreased 1 cm and there were no significant neurologic signs or symptoms. A progressive improvement in skin color occurred and three weeks after admis-

sion there was no increased pigmentation. Hemoglobinuria disappeared completely after two days and there was no recurrence. At the end of the first hospital week the NPN was 28 mg per 100 ml.

At discharge, three weeks after admission, the infant was quite normal in appearance and weighed 3700 g. There were no signs of intracranial hypertension. Neurological examination, including electroencephalography and ophthalmoscopy, revealed no abnormalites. There were no signs of renal damage. When the child was last seen, at the age of three months, he appeared to be quite healthy and was developing normally.

Summary of clinical findings.—A 9-day-old infant was admitted with a history of vomiting, fever, lethargy and increased intracranial pressure of three days' duration, preceded by no abnormalities other than a moderate cephalhematoma. Examination disclosed hemoglobinuria, hemoglobinemia and high concentrations of methemalbumin in the serum and spinal fluid. There was no significant hyperbilirubinemia and no evidence of a high rate of red blood cell destruction. Although it was never possible to rule out a urinary tract infection with absolute certainty, there was no real evidence of sepsis. The child improved spontaneously and appeared normal after a three-week hospitalization.

Identification of the Heme Pigments and Studies of their Metabolism

Some of the clinical features which this patient exhibited on admission were those of a preceding intravascular hemolytic episode. Because of the possibility that such signs as the skin pigmentation and increased intracranial pressure might be secondary to an accumulation of abnormal heme pigments, steps were taken to identify the pigments present in the body fluids and to study their metabolism.

Methods.—The methods employed were those described in a previous publication (cf. Zetterström, Stempfel & Escardó).

Identification of the heme pigments.—Fig. 1 shows spectrophotometric absorption curves from serum and urine obtained on admission. A typical oxyhemoglobin absorption spectrum was obtained from the urine, with peaks at 412, 540 and 575 mμ. The serum, on the other hand, showed peaks at 405, 535, 575 and 620 mμ, in addition to a slight elevation at 460 mμ. The difference between the spectra lies, therefore, in the presence of 620 and 460 mμ peaks. The former represents methemalbumin (hematin bound to serum albumin) and the latter, serum bilirubin. Methemalbumin is characterized by a major absorption peak at 405 mμ and minor peaks at 500, 540 and 623 mμ (Rosenfeld & Surgenor). In sera containing both this pigment and oxyhemoglobin, the alpha-band of methemalbumin at 620–623 mμ is of primary importance in detecting that pigment by direct spectrophotometry.

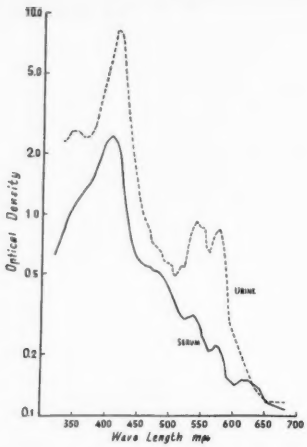

Fig. 1. Spectrophotometric absorption curves from undiluted urine (upper curve) and from serum diluted 1:20 (lower curve), on admission. In the urine, 3 peaks were apparent: 415 mμ, 540 mμ and 570 mμ, corresponding to the spectrum of oxyhemoglobin. The absorption curve obtained from serum revealed 5 peaks: 405 mμ, 460 mμ, 540 mμ, 570 mμ and 620 mμ. The peaks at 405 mμ and 620 mμ represent methemalbumin. Bilirubin is responsible for the peak at 460 mμ.

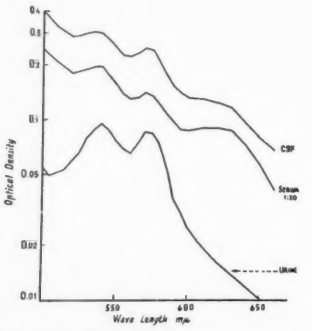

Fig. 2. Spectrophotometric absorption curves from undiluted CSF, serum diluted to 1:20 and undiluted urine, 12 hours after admission. The CSF and serum curves are of identical configuration, indicating the presence of the same pigments in both and in similar proportions. The absorption curve from the urine corresponds to that of oxyhemoglobin.

Fig. 2 shows the absorption curves of corresponding serum, cerebrospinal fluid and urine samples in a part of the visible spectrum. A comparison of the curves from diluted serum and cerebrospinal fluid shows that they are of almost identical configuration, indicating that those pigments present in the serum are also present in the cerebrospinal fluid in almost the same proportion. It is clear that, while methemalbumin crossed the blood–spinal

Fig. 3. Stained and unstained paper electrophoretic strips illustrating heme pigment attachment to the albumin fraction after separation of the serum proteins.

fluid barrier, serum concentrations did not exceed the renal threshold and the pigment never appeared in the urine in detectable quantitites.

The presence of hematin in the serum was verified by means of the Schumm test. On paper electrophoresis a heme compound was found to migrate with the albumin fraction, as is shown in Fig. 3. In order to determine the migration of the albumin-bound pigment and the proportion of this pigment to the other heme compounds, an unstained strip from a serum sample was sectioned after electrophoresis according to protein separation determined from a duplicate stained strip which was run in parallel. The samples shown in Fig. 3 were obtained about 20 hours after admission. The total hemochromogen content in each section was measured as described by Tuttle, using the benzidine test. With this method, the heme compounds were found to be almost quantitatively localized in the same area as the albumin fraction. In sections corresponding to the globulin fractions, only traces of pigment were found. Since hematin is the sole heme pigment bound to serum albumin (Fairley), the major heme pigment present in the sample was methemalbumin.

Metabolism of the heme compounds.—On admission, analysis revealed a serum total hemochromogen concentration of 310 mg per 100 ml (method of Wu, as modified by Bing and Baker (cf. Ham)), of which the major portion was methemalbumin. Hemoglobin and methemalbumin both appeared in the cerebrospinal fluid and here the total hemochromogen content was 45 mg

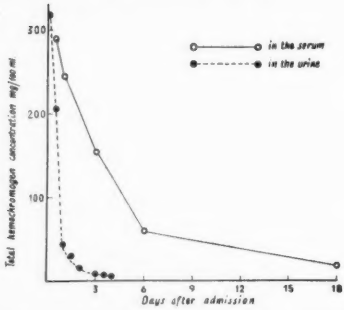

Fig. 4. Total hemochromogen concentration of the serum and of 12-hour urine specimens during the period of observation. There was a relatively slow disappearance of heme pigments from the serum. The urinary excretion of heme compounds, on the other hand, had almost ceased within 4 days.

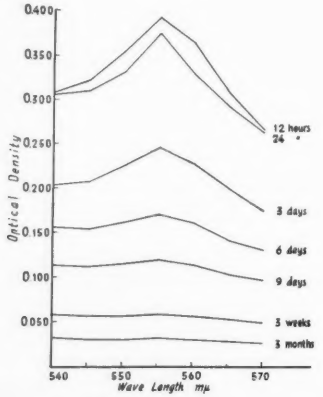

Fig. 5. Absorption curves showing the results of the Schumm test on repeated serum samples. The appearance of a peak at 555 mμ was a positive test for the presence of methemalbumin in the first 6 samples. The test was negative in the last sample, illustrating the disappearance rate of methemalbumin.

per 100 ml. In the urine, however, oxyhemoglobin was the only heme compound which was present in detectable quantities.

During the hospital course there was a rapid decrease in the urinary hemochromogen concentration, as is shown in Fig. 4, and after a three-day period the urine was almost oxyhemoglobin-free. However, the heme pigments disappeared very slowly from the serum, and 18 days after admission there was still a significant elevation of the total heme pigment concentration.

Fig. 5 illustrates the absorption of diluted serum samples after the addition of Schumm reagent at intervals throughout the course. As may be seen from

TABLE 1

Metabolism of heme compounds.

	Serum concentration (mg per 100 ml)			Urinary excretion of hemoglobin (mg per 12 hrs.)
	Total hemochromogen	Methemalbumin	Hemoglobin	
After 12 hours . . .	310	252	58	290
24 ,, . . .	244	216	28	59
36 ,, . . .				46
48 ,, . . .				15
3 days . . .	155	132	23	12
6 ,, . . .	62	62	0	0
9 ,, . . .		36		
18 ,, . . .	19	10		
3 months . .	10	0		

this figure, there was a progressive decrease in the absorption peak at 555 mμ (the methemalbumin peak after addition of Schumm reagent) during the period of hospitalization. Twenty-one days after admission there was still a slight peak which was no longer apparent 2 months later. The absorption curves shown in Fig. 4 indicate the high serum total hemochromogen level on admission which, similarly, underwent a slow but progressive decrease.

After electrophoretic separation of the serum proteins, determination of the proportion between the various heme-protein pigments revealed that only methemalbumin remained in measurable quantities on the third hospital day.

On the sixth hospital day, the total hemochromogen concentration was found to be 62 mg per 100 ml. Since, on that occasion, the serum heme pigment consisted almost entirely of methemalbumin, rough determinations of the serum methemalbumin level were estimated from the spectrophotometric absorption curve which appeared after the addition of Schumm's reagent (cf. Zetterström *et al.*). Methemalbumin concentrations determined using this method are included in Table 1.

Methemalbumin, which had reached extremely high levels on admission, underwent a progressive decrease. When those serum hemochromogens which could not be identified as this pigment are considered to be hemoglobin, it will be noted that the serum hemoglobin level was relatively low 12 hours after admission and that this concentration underwent a further rapid decline. Therefore, the hemolytic activity had ceased prior to hospital admission.

Comment

The marked hemoglobinuria and high methemalbumin concentration in the presence of a low serum bilirubin level and an almost normal blood hemoglobin concentration indicate that there was no massive hemolysis. During the acute hemolytic episode, most of the red-cell destruction seems to have been intravascular, hemoglobin having been released directly into the plasma.

Hemoglobinuria occurs when the plasma concentration exceeds the renal threshold for hemoglobin which is normally at about 130 mg per 100 ml. In certain conditions, however, it may be lower and in paroxysmal nocturnal hemoglobinuria, or in any chronic hemoglobinuria, it often lies between 50 and 100 mg per 100 ml (Yuile).

In the case described here, the cause of the intravascular hemolytic process giving rise to hemoglobinemia and hemoglobinuria is obscure, and although there was fever on admission, there were no other indications that sepsis was a factor. That the cephalhematoma could have been the major source of free heme pigment is another possibility worthy of consideration. The clinical features resembled those seen in paroxysmal hemoglobinuria, although subsequent exacerbations were not observed. On admission, intravascular hemolysis had ceased and free hemoglobin disappeared within a few days. It would appear that the disappearance rate of methemalbumin from the plasma provides reliable information concerning the rate at which an intravenous load of this pigment would be metabolized in the patient studied. From experiments where alkaline hematin was injected intravenously into normal adults, Fairley concluded that methemalbumin, formed after the injection, is metabolized within 36 hours, probably by the reticuloendothelial system. In liver disease, however, he found a marked reduction in the rate at which methemalbumin disappeared from the circulation. It would seem, then, that hepatic damage or hepatic immaturity may have been a major factor in the present case, but it will be noted that, clinically, there were no other indications of disturbed liver function and multiple paper electrophoretic separations of the serum proteins and bilirubin partition were not remarkable in this regard. Because methemalbumin sometimes appears in the plasma of apparently normal infants at birth and in extremely high plasma concentrations in infants with hemolytic disease of the newborn (Tuttle; Zetterström, Stempfel & Escardó), it is probable that there is a low capacity for metabolizing this pigment in the neonatal period.

To what extent methemalbumin may be toxic in man is far from clear. Crosby has stated that convulsive disorders as well as psychotic episodes are common in paroxysmal nocturnal hemoglobinuria. Symptoms referable

to the central nervous system may also be caused by the accumulation of abnormal heme compounds.

It is probable that methemalbuminemia of the degree present in the case reported here is extremely rare. Whether the clinical picture, excluding skin coloration, can be explained solely on the basis of the presence of this pigment in the serum is questionable. However, the appearance of measurable amounts of methemalbumin in the spinal fluid indicates that the pigment may cross the blood–spinal fluid barrier and it seems reasonable to assume that it may have been implicated in the production of intracranial hypertension which disappeared as the pigment was metabolized.

Summary

The clinical findings in a newborn infant who developed idiopathic transient hemoglobinemia associated with hemoglobinuria and intense methemalbuminemia are described.

Marked skin pigmentation was present which was thought to be secondary to methemalbumin accumulation. This pigment appeared in the cerebrospinal fluid but was not excreted in the urine. The possible role of methemalbumin in the production of intracranial hypertension is discussed.

Serum pigments were investigated by means of paper electrophoresis and spectrophotometry in addition to quantitative estimations of methemalbumin and free hemoglobin in the serum and cerebrospinal fluid.

The slow rate of disappearance of methemalbumin from the plasma suggests that a diminished capacity to metabolize this pigment exists in the neonatal period.

Hémoglobinémie passagère associée à une hémoglobinurie et une «méthémalbuminémie» au cours de la période néo-natale.

Les auteurs rapportent l'histoire clinique d'un nouveau-né présentant une hémoglobinurie passagère associée à une hémoglobinémie et une «méthémalbuminémie» sévère. L'accumulation de «méthémalbumine», sa lente élimination du sérum, ont été atribuées à une capacité défectueuse de son métabolisme au cours de la période néo-natale. Le pigment s'est montré capable de diffuser dans le liquide céphalorachidien, mais pas d'être éliminé par l'urine. La peau a pris une teinte marron-bronzée, qui a disparu quand le niveau sanguin de «méthémalbumine» a diminué. L'episode d'hypertension intracranienne avec hyperproduction de LCR a été attribué à un effet toxique de la part de la «méthémalbumine» Les pigments sanguins ont été investigués par l'électrophorèse en papier et la spectrophotométrie. Des determinations quantitatives ont été faites dans le LCR et le sérum pour mesurer la «méthémalbuminémie» et l'hémoglobine.

Vorübergehende Hämoglobinämie in der Neugeburtsperiode mit Hämoglobinurie und Methämalbuminämie.

Es werden die klinischen Befunde eines Neugeborenen besprochen, das an idiopathischer vorübergehender Hämoglobinämie mit Hämoglobinurie und intensiver Me-

thämalbuminurie litt. Es waren ausgeprägte Hautpigmentationen, vermutlich als sekundäre Folge der Methämalbuminanhäufung, vorhanden. Dieses Pigment erschien in der Cerebrospinalflüssigkeit, wurde aber nicht mit dem Urin ausgeschieden. Die Rolle, die das Methämalbumin möglicherweise bei der Produktion eines intracranialen Überdruckes spielt, wird besprochen. Die Serumpigmente wurden mit Hilfe von Elektrophorese und Spektrophotometrie in Verbindung mit quantitativen Bestimmungen des Methämalbumins und des freien Hämoglobins im Serum und der Cerebrospinalflüssigkeit bestimmt. Das langsame Verschwinden von Methämalbumin aus dem Plasma lässt vermuten, dass in der Neugeburtsperiode eine herabgesetzte Fähigkeit zum Abbau dieses Pigmentes besteht.

Hemoglobinemia pasajera asociada con hemoglobinuria y metahemalbuminuria en el período neonatal.

Se describen los hallazgos clínicos en un lactante que presentó una hemoglobinemia cuyo origen no fué posible precisar asociada con hemoglobinuria e intensa metahemalbuminemia. La acentuada pigmentación de la piel fué interpretada como secundaria a la acumulación de metahemalbuminemia. El pigmento apareció en el líquido cefalorraquídeo pero no en la orina. Se discute el posible rol de la metahemalbúmina en la producción de hipertensión intracraneana. Los pigmentos séricos fueron investigados por medio de la electroforesis en papel y espectrofotometría realizándose además determinaciones cuantitativas de metahemalbúmina y hemaglobina libre en suero y LCR. La lenta desaparición de la metahemalbúmina del plasma sugiere una capacidad disminuída para metabolizar este pigmento durante el período neonatal.

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Glycogen Storage Disease of the Liver

Report of an Atypical Case with Studies of the Glycogen Structure and the Glucose-6-phosphatase Activity of the Liver

by ROLF ZETTERSTRÖM and BO SÖRBO

Glycogen storage disease can, according to G. Cori, be divided into four pathogenetically different entities. The most frequently occurring hepatic type, i.e. von Gierke's disease, which by earlier workers in this field (van Creveld; Mason & Andersen) had been assumed to be caused by enzymatic dysfunction, has been demonstrated by Cori & Cori to originate from a deficiency of the enzyme glucose-6-phosphatase in liver and kidneys. Two other types of glycogen storage disease of the liver have been described by G. Cori. Both were characterized by the presence of abnormal glycogens, which probably were formed due to the lack of branching and debranching enzyme, respectively. In the fourth type of glycogen storage disease, i.e. in generalized glycogenosis with cardiac involvement (Pompe's disease) it has not been possible to demonstrate any enzyme deficiency and the glycogen does not differ from normal human glycogen. Polglase, Smith & Tylor demonstrated from the sedimentation rate in the ultracentrifuge the presence of an abnormal glycogen in a case of glycogenosis with predominantly muscular involvement. This might indicate the existence of still another type.

In this report a clinically atypical case of glycogen storage disease of the liver will be described. There was a high glycogen content in the liver but the glycogen structure was found to be normal, and there was no glucose-6-phosphatase deficiency.

Case Report

J. O. C., a 12 year old boy, was admitted to the Pediatric Clinic, Karolinska Sjukhuset, because of hepatomegaly and a respiratory tract infection.

He was the first child of healthy parents. The family history was negative. Birth-

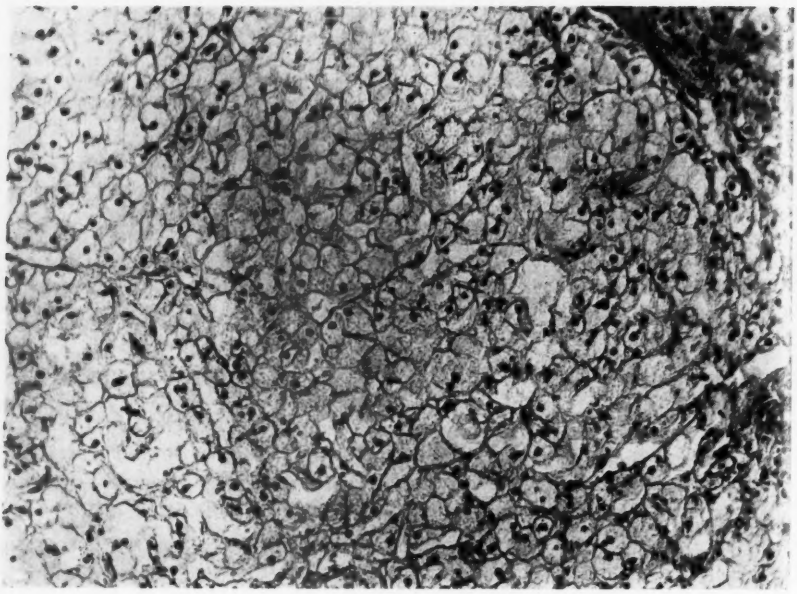

Fig. 1. Section of liver stained with hemotoxylin and eosin. Enlargement of the hepatic cells and vacuolisation is evident. 250 ×.

weight 3960 g. He was breastfed for the first 8 months of life. When 9 months old he was admitted to a children's hospital because of hepatomegaly and bad weight gain. The infant who was slightly under weight with a weight of 7,300 g had an enormous hepatomegaly and a slight splenomegaly. The fasting blood sugar level was found to be lower than normal (varying between 60 and 80 mg per 100 ml). There was a normal adrenalin tolerance test (the blood sugar level rose from 63 to 128 mg per 100 ml within one hour). Glycogen storage disease of the liver was suspected because of the histologic findings (Fig. 1).

At the age of 7 years the patient had been admitted to another hospital because of bronchopneumonia. His mental development was normal. He was very thin and short of stature, with a weight of 19.5 kg and a length of 110 cm. The liver almost filled the whole abdomen and there was a moderate splenomegaly. The fasting blood sugar level was normal. On adrenalin tolerance test the blood sugar level rose from 120 mg to 180 mg per 100 ml within one hour. A massive acetonemia and acetonuria developed one hour after the administration of adrenalin. The next morning the urine was free of acetoacetate. A double glucose tolerance test was of a diabetic type with failing Staub effect.

The patient was sent to this clinic when he was 12 years old because of a respiratory tract infection. He was said to have been in a relatively good condition since his last stay in hospital. Periodically severe anorexia occurred. There were no problems in school.

Fig. 2. Photo of the patient at an age of 12 years. The enormous hepatomegaly is evident.

On admission the physical examination revealed a very thin, dwarfish, physically underdeveloped 12 year old boy with a big abdomen (Fig. 2). His mental development seemed to be normal. His length was 130 cm and the weight was 27.4 kg. There were symptoms of a throat infection with bronchitis. Heart auscultation was normal. The liver was felt below the umbilical level and was very firm in consistency, and the spleen was felt 4 cm below the costal margin. Roentgenograms of heart and lungs and of the whole skeleton were normal. Electrocardiography did not reveal any abnormalities. The electroencephalogram was slightly dysrhythmic. The eye grounds were normal and no cataract was found.

The hemoglobin level was 11.8 g per 100 ml and there were 5,300 white cells per cmm. The serum electrolytes were within normal limits. The serum bilirubin level was 0.80 mg per 100 ml, and alkaline phosphatase activity was 12 units per 100 ml. The total serum protein level was 7.2 g per 100 ml, and the electrophoretic separation of the serum proteins showed a normal pattern except for a slightly elevated α_2-fraction (14 per cent).

Thymol turbidity test was high, 8.1 units. The total serum lipid level was 1055 mg per 100 ml and the cholesterol level 256 mg per 100 ml. There was no proteinuria, and the urine did not contain casts or red cells. NPN was normal, and there was no polyuria.

Three weeks after admission a laparotomy was performed, and a liver biopsy was taken.

Histologic examination of formalin fixed liver tissue revealed a highly abnormal picture. The hepatic cells were greatly enlarged, and cytoplasm and nuclei were vacuolised. In ethanol fixed tissue carmine stain of Best revealed a massive granular deposition of stainable material in the cytoplasm and, to a slight extent, in the nuclei. This material disappeared after incubation with diastase. Big fat vacuoles were abundant. Deeply staining material was also seen in the periodic acid stain.

Studies of Carbohydrate Metabolism

Glucose metabolism.—The fasting blood sugar level varied between 77 and 149 mg per 100 ml, thus there was no real hypoglycemia. The blood sugar level was labile, varying between 77 and 220 mg per 100 ml during one day and a postalimentary hyperglycemia was noted.

An oral glucose tolerance test (1 g of glucose per kg body-weight was administered) showed a reduced tolerance. The fasting level was 100 mg per cent, after 39 minutes it was 183 mg per cent, after 90 minutes 178 mg per cent, and after 180 minutes 101 mg per cent. No reducing substance was found in the urine. A double glucose tolerance test showed no Staub effect.

The administration of adrenalin caused a rise of the blood sugar level from 75 mg per cent to 108 mg per cent. After the administration of adrenalin, the patient developed acetonemia, and there was a high urinary output of acetoacetate. Otherwise, there were only occasionally traces of acetoacetate in the urine.

Fructose metabolism.—The injection of 25 g fructose caused a rise of the blood sugar level from 95 mg % to 140 mg % within one hour. Whether this test can be considered as a proof of an impairment of cellular fructose utilization is, however, difficult to evaluate.

Enzymatic studies.—Liver specimens which had been obtained on biopsy were immediately frozen down with the aid of solid carbon dioxide after the removal. The specimens were stored in a freezer at –20° C until analysed, usually within 2 months.

The glucose-6-phosphatase activity of liver tissue was investigated in the patient with glycogen storage disease and in two other patients without known liver disease. In the control cases, which were 11 and 12 years, laparatomy was performed because of acute surgical indications. After homogenisation of the liver specimen in cold water, glucose-6-phosphatase activity was determined in exactly the same way as described by Cori & Schulman. As is shown from Table 1 the glucose-6-phosphatase activity was found to be almost as high as in the liver specimens from the control cases. The values agree with those reported by Cori as the normal liver activity. It might be assumed that the slightly decreased activity in the

TABLE 1.

Glucose-6-phosphatase activity in liver homogenate in the patient with glycogen storage disease of the liver.

Amount of liver tissue in the homogenate mg	Amount of P liberated in 1 hour at 30° μg	Amount of P liberated per 100 mg liver μg
21	666	317
10.5	333	317
5.25	173	330
2.6	92	350

In two patients without known liver disease liver biopsy specimens obtained on laparotomy performed for other reasons liberated in 1 hour 450 and 490 μg of P per 100 mg liver from glucose-6-phosphate, respectively.

liver of the patient when compared with the normal ones can be due to a lower amount of cells per unit of weight in this liver specimen owing to the high fat and glycogen content.

Studies on the Hepatic Glycogen

Determination of glycogen in a liver biopsy specimen was carried out according to Good, Kramer & Somogyi and gave a glycogen content of 11.7 per cent. From a part of the biopsy specimen, immediately frozen down with solid carbon dioxide, the glycogen was purified according to Polglase, Smith & Tyler. A 1 per cent solution of the purified material in 1*M* NaCl was then investigated in the Spinco analytical ultracentrifuge Model E. From the ultracentrifuge sedimentation pattern obtained, as shown in Fig. 3, it is evident that only one component was present in the preparation. As $S_{20,w}$ was determined to 83.5 × S, this component must be identical with the lighter component found by Polglase, Smith & Tyler in normal liver glycogen. The normal liver glycogen was found by these authors to contain also a heavier component with $S_{20,w}$ = 150–300 × S, but no heavy component was detected in the present case. Of interest in this connection is that Polglase, Smith & Tyler reported that liver glycogen from a case of von Gierke's disease only consisted of the lighter material.

The iodine absorption spectrum of the purified glycogen was also determined according to Illingworth & Cori. A normal spectrum with a peak at 470 mμ was obtained, demonstrating that glycogen with an amylopectin structure was absent from this preparation. No abnormality in the structure was thus demonstrated.

Fig. 3. Sedimentation pattern of a liver glycogen sample. One per cent solution in 1*M* NaCl, speed 19,160 r.p.m., time interval between exposures 8 minutes.

Discussion

Some of the clinical features of the patient described were those observed in glycogen storage disease of the liver. The histological findings from a liver biopsy specimen and the demonstration of a high glycogen content in the liver are also consistent with this diagnosis. The unusual height and prolongation of the blood sugar curve and the lack of a Staub effect are also commonly found in von Gierke's disease (cf. Mason & Andersen). However, the normal or only slightly decreased fasting blood glucose level and a normal increase of the blood sugar level after the administration of adrenalin, demonstrated on several occasions are atypical.

The cause of the disease cannot be deduced from the results obtained. The almost normal glucose-6-phosphatase activity of the liver appears to rule out a deficiency of this enzyme. Furthermore, the studies of the glycogen structure did not reveal any differences from normal human liver glycogen. The finding of a normal fasting blood sugar level and a normal response to adrenalin seems to be in accord with the demonstration of normal glucose-6-phosphatase activity of the liver, since this enzyme apparently is of utmost importance for the prevention of hypoglycemia (cf. de Duve). Undoubtedly there is, in our case, a metabolic block in carbohydrate metabolism as revealed not only by the intense accumulation of acetone bodies after the administration of adrenalin, but also by other findings. The investigations performed do not permit a localization of this probable block. The finding of a probably normal glycogen structure and of an impaired fructose utilization may indicate that it is situated below the aldolase level. This suggestion naturally does not exclude the possibility of a localization higher up in the glycogenolytic pathway.

The studies of the case reported suggest that there might be other metabolic defects causing glycogen storage disease of the liver beside the formation of abnormal glycogens or a glucose-6-phosphatase deficiency. G. Cori (in her review) reported two cases with a typical von Gierke's disease but with almost normal glucose-6-phosphatase activity of the liver. Both these

cases were not severely affected by their disease and had grown up nearly to adolescence. It does not seem unlikely to assume that the cause of the disease was the same in those two cases as in our patient.

Summary

The course and clinical features in a 12 year old boy with a glycogen storage disease of the liver with some atypical findings have been described. No significant hypoglycemia was present and the response to adrenalin was normal. The liver glycogen structure was found to be normal and the glucose-6-phosphatase activity was only slightly decreased. The significance of these findings has been discussed and it is concluded that other types of hepatic glycogenosis exist beside those caused by a glucose-6-phosphatase deficiency or the formation of abnormal glycogens.

La glucogénose du foie — A propos d'un cas atypique avec étude de la structure du glycogène et de l'activité de la glucose-6-phosphatase dans le foie.

Les aspects cliniques et l'évolution chez un garçon de 12 ans d'une glycogénose du foie présentant quelques traits inhabituels sont décrits. Il n'existait pas d'hypoglycémie et la réponse à l'adrénaline était normale; la structure du glycogène hépatique était non modifiée, et l'activité de la glucose-6-phosphatase légèrement diminuée. La valeur de ces constatations est discutée. La conclusion est qu'à côté des glycogénoses par insuffisance de la glucose-6-phosphatase ou par formation d'un glycogène anormal, il est certainement d'autres types.

Glykogenspeicherkrankheit der Leber. Bericht eines atypischen Falles mit Untersuchungen der Glykogenstruktur und der Glukose-6-Phosphatase der Leber.

Der Verlauf und die klinischen Merkmale eines 12 Jahre alten Jungen mit Glykogenspeicherkrankheit der Leber mit einigen atypischen Befunden werden beschrieben. Es war keine bedeutende Hypoglykämie vorhanden und die Reaktion auf Adrenalin war normal. Die Struktur des Leberglykogens wurde normal befunden und die Glukose-6-Phosphatase-Aktivität war nur leicht herabgesetzt. Es wird die Bedeutung dieser Befunde erörtert und der Schluss gezogen, dass andere Typen von Hepatoglykogenosis vorkommen neben denen, die durch einen Glukose-6-Phosphatase-Mangel oder die Bildung von abnormem Glykogen bedingt sind.

Glicogenosis hepática. Relato de un caso atípico y estudios sobre la estructura del glicógeno y la actividad de la glucosa-6-fosfatasa.

Se relata el curso clínico y hallazgos, algunos de ellos atípicos, en un paciente de 12 años portador de una glicogenosis hepática. El glicógeno hepático y la respuesta a la adrenalina fueron normales, hubo una actividad de glucosa-6-fosfatasa apenas disminuída y la hipoglicemia no fué significativa. Se discute la significación de estos hallazgos concluyendose que además de glicogenosis hepáticas causadas por deficiencia de glucosa-6-fosfatasa o por formación anormal de glucosa, existen otros tipos de esta afección.

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Respiratory Studies in Children

I. Lung Volumes in Healthy Children, 6–14 Years of Age[1]

by INGA ENGSTRÖM, PETTER KARLBERG and SVEN KRAEPELIEN

Although an abundance of different lung function tests are used at present in various cardiopulmonary diseases in adult medicine, these tests have been applied in pediatrics only to a very limited extent. As respiration is not a simple isolated function but is composed of a complex of many interrelated factors, there is as yet no single test which can give a complete picture of the respiratory state. Therefore, each respiratory component must be studied separately. Such studies can be applied to four main subjects: (1) *Lung volumes;* (2) *ventilation*, including volume and distribution of air ventilating the alveoli; (3) *diffusion*, through alveolar-capillary membranes; and (4) *circulation*, chiefly the pulmonary capillary blood flow.

Up to the present time the principal lung function test which has been used for children has been the determination by simple spirometry of lung volumes, especially the vital capacity with its subdivisions. Reports of vital capacity in children have been published by Wintrich already in 1854 (quoted by Püschel); but in the nineteen-twenties the results of careful studies on large groups of children first appeared in the literature (Emerson and Green; Wilson and Edwards; Stewart; Baldwin; Serebrowskaja). Interest in the subdivisions of the total capacity began to increase in the nineteen-thirties when methods were developed for measuring the residual volume of adults. The first residual volume determinations performed on children which we have been able to find in the literature appeared in 1938 (Robinson). Since that time only one account of a similar study has been published (Morse *et al.*). In the two investigations concerned with residual volumes, Robinson studied 29 boys of only three ages (6, 10 and 14 years); and Morse *et al.*, 94 boys between the ages of 10 and 17 years. Both authors used the closed circuit O_2 method of Christie, which has later been criticized and modified. Because so little has been done in this field, it has seemed necessary to begin our planned respiratory studies to determine lung volumes of both boys and girls by using a method more suitable than earlier ones.

[1] Aided by a grant from The Swedish Association against tuberculosis.

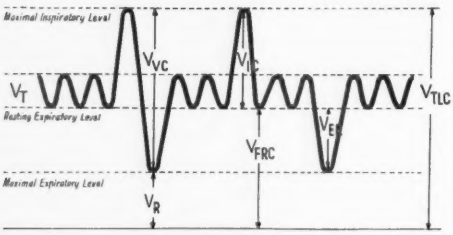

Fig. 1. Lung volumes.

V_T = Tidal volume
V_{ER} = Expiratory reserve volume
V_R = Residual volume
V_{IC} = Inspiratory capacity
V_{FRC} = Functional residual capacity
V_{VC} = Vital capacity
V_{TLC} = Total lung capacity

Definitions and Nomenclature

For definitions of these lung volumes, reference may be made to the recently published monograph, *The Lung*, by Comroe *et al.* The different volumes are shown graphically in Fig. 1, in which the nomenclature is that proposed by a group of American clinical and research respiratory physiologists headed by J. R. Pappenheimer.

Material

Ninety-three healthy children from 6–14 years of age were studied, 50 boys and 43 girls. Of these, 25 were from 6 to 8 years of age; 31, from 9 to 11 years; and 37, from 12 to 14 years (see Figure 7). Most of the children were chosen by nurses in schools and child welfare centers. A small number were children who had visited this clinic for reasons which would not have any effect on their lung function. The children's physical development was judged from Broman, Dahlberg and Lichtenstein's normal values for Swedish children. These apply to the relation of length to age and of weight to length. For the two relationships there were only four and one, respectively, of the 93 children in the present study whose measurements fell outside of the 95 per cent confidence limits.

Methods

A closed circuit method with helium as the test gas was used (Meneely and Kaltreider, 1941 and 1949; Willmon and Behnke; Gilson and Hugh-Jones; Holmgren), and the system's volume was kept constant by continuous addition of oxygen (Herrald and McMichael). The advantages of this method are that the end-expiratory position can easily be determined from the record and alveolar gas analyses do not have to be done, facts which are of great importance in determinations on children whose cooperation cannot always be assured. Another advantage is that one always knows when complete mixing is established in the system after connection of the child's airways. Moreover, the method is simple to perform.

Apparatus and procedure.—The closed system (Fig. 2) consists of the following parts, coupled in series: a spirometer (Benedict-Roth type, 5 liter capacity); a water-lock for adding helium, O_2 and air to the system; a double valve composed of two disks sliding over each other, allowing the child to breathe air from outside the system in one valve position and the system's gas in the other; a circulating pump (fan type

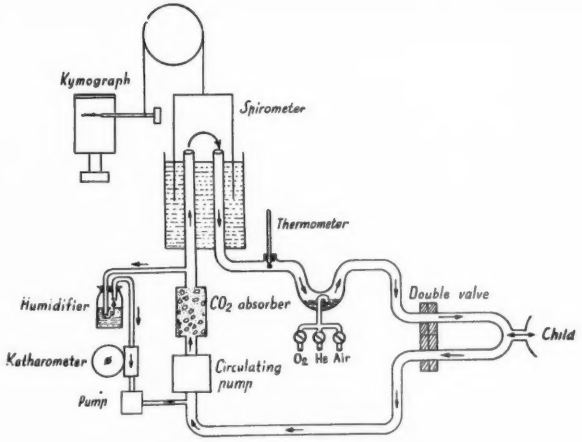

Fig. 2. Diagram of apparatus.

with a capacity of about 30 liters/min.); and a CO_2 absorber. A humidifier, a Cambridge helium katharometer (reading range = 0–20 vol. per cent, and reading accuracy = $\pm$ 0.1 vol. per cent[1]), and a small membrane pump (1–2 liters/min. capacity) are connected in a shunt across the circulating pump and the CO_2 absorber. The system's fixed volume with the spirometer at its lowest position was made as small as possible (1.43 liters). The water level in the spirometer is always kept at a certain mark on a water gauge. The child breathes through a mouthpiece, while the nose is closed with a nose clip. The mouthpiece is connected with the system via two tubes (about 80 cm long) through the double valve. This makes it possible for the child to get used to breathing through the mouthpiece before the determination begins. It has been very helpful to have the connecting valve placed at a distance from the child, because the mouthpiece with its connections can be made light and flexible and can be hung so that it may move freely in the horizontal plane. The child can be connected with the system without his noticing the change. The volume of the two tubes and the mouthpiece mentioned above will thus be added to the functional residual capacity (V_{FRC}). However, this volume is always constant. During the time when the child is getting adapted to breathing through the mouthpiece, the circulation in this little open system is ventilated through one of the connecting tubes by a stream of air from a tank (approximately 30 liters/min.).

Before the child comes into the laboratory, the system is washed out for a few minutes with fresh air driven through it by the circulation pump. The system is then closed at the double valve, and helium, O_2 and air are added by way of the water-lock in such proportions that the helium concentration in the gas mixture will be about 19–20 vol. per cent and the O_2 concentration about 21 vol. per cent.

The gases are mixed by the circulation pump, and katharometer readings of the helium concentration show when equilibrium is reached. In order to decrease the error of the determinations as much as possible, the volume of the gases added to the

[1] For construction of katharometer and for reading technique, see Meenely and Kaltreider (1949) and Holmgren.

closed system should be so adjusted before connecting the child that the helium concentration with the child connected decreases by 40–50 per cent of the initial value, after equilibrium is reached (Björklund and Dahlström).

It is a good rule to make these preparations before the child arrives, in order not to disturb him too much. During the determination the child is sitting in a comfortable chair with his feet on a foot rest. He should be resting there for 15–20 minutes before the determination is started. After the initial helium concentration is carefully read and the child is breathing quietly, the spirometer kymograph is started and the child is connected with the system. This must be done as close to the end-expiratory position as possible. A connection at exactly this time is not necessary, however, for a certain correction must usually be made because the final recorded end-expiratory level is frequently not exactly the same as that at the beginning (see Calculations). Oxygen is added continuously in order to keep the volume of the system as constant as possible. The helium concentration is read every minute (± 5 sec.). When constant readings during even breathing and the maintenance of a constant volume have been obtained for 3–4 minutes, there is enough information for calculating the subject's V_{FRC}. A change during the determination of 150 ml or less in the closed system's volume does not invalidate the results. A volume change of this magnitude, causing a small change in the O_2 concentration, gives an error in the reading of the helium concentration which is only within the katharometer's accuracy (Holmgren).

After this, determinations are made of the vital capacity (V_{VC}) and its subdivisions, the expiratory reserve volume (V_{ER}) and the inspiratory capacity (V_{IC}). For this, the child is first strongly encouraged to make a maximal expiration and then, after about one minute's ordinary breathing, a maximal inspiration. The V_{VC} is calculated later by adding the values for V_{ER} and V_{IC} thus obtained. This procedure was chosen because it has seemed easier for children to produce a maximal expiration from a resting respiratory level than immediately after a maximal inspiration. This is particularly the case in smaller children and in pathological cases. For the calculations it would be ideal to wait each time until even breathing is established again before forced breathing is once more undertaken. It is not practical to do this, however, as doing the determination in that way would take too long and make the child unhappy. Therefore, an interval of about one minute is used between forced breaths. The procedure described for obtaining V_{ER} and V_{IC} is repeated three times.

After the child has rested for 10–15 minutes, a second complete determination is made.

Calculation of V_{FRC}. — The child's functional residual capacity is calculated according to the formula:

$$V_{FRC} = \left[\frac{(V_L + V_S)\,(F_{\text{He I}} - F_{\text{He II}})}{F_{\text{He II}}} - M \pm C \right] r.$$

V_L = the fixed volume of the system, with the spirometer at its lowest position (1.43 liters).

V_S = the initial recorded volume of the spirometer before the child is connected (see Fig. 3).

$F_{\text{He I}}$ = the initial helium fraction.

$F_{\text{He II}}$ = the final helium fraction after gas equilibrium has been established.

M = constant volume of mouthpiece and tubes up to the double valve (0.48 liters).

C = correction for possible difference between the initial volume of the spirometer and the end-expiratory position after gas equilibrium has been established.
r = factor for correcting to BTPS.

The first part of a typical respiratory record is shown in Fig. 3. From this it may be seen how the correction (C) is determined. No correction has been made for absorption of helium by the blood during the determination (Holmgren).

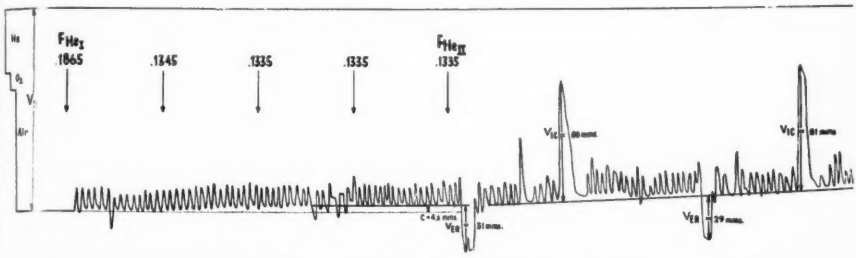

Fig. 3. One respiratory record. The initial baseline and the end-expiratory position for the calculation of the functional residual capacity (V_{FRC}) are shown. The difference between the lines $= C$. The fractions of helium (F_{He}) are marked at one-minute intervals. The volumes V_{IC} and V_{ER}, may be obtained by multiplying the measured deflections in millimeters by the calibration of the spirometer.

Calculations of V_{VC} and its subdivisions.—Because the child must do increased work during forced breathing and will often be made somewhat uneasy, the O_2 consumption will be slightly increased. This can be noticed on most of the curves. The recorded end-expiratory position on the kymograph paper will therefore be successively raised. To compensate for this by increasing the amout of O_2 added to the system has proved difficult. The V_{ER} and V_{IC} have therefore been measured from the best line that can be drawn on the record along the end-expiratory points (Fig. 3). The mean values of the two largest recorded V_{ER}'s and V_{IC}'s have been used; but, as the V_{ER} and V_{IC} are reached at the maximum forced ex- and inspirations, respectively, the largest value of each should be the correct one to use. However, since the recording error in most determinations could be at least as big as the variation in the voluntary effort of the forced breathing, the mean of the two largest values has been chosen.

The V_{ER} and V_{IC} have been corrected to BTPS from the temperature of the system. This might not be quite correct, as, during the relatively short time involved, the temperature of the forced expired air cannot immediately fall to the system's temperature. On the other hand, the temperature of the forced inspired air must rise fairly rapidly. Most authors have thus chosen this way of correcting, and it seems to involve the least error. Some authors, however, are making a temperature correction only for the V_{FRC} (Herrald and McMichael; Whitfield *et al.*).

Calculations of the different lung volumes.—The following equations are used:

the vital capacity, $V_{VC} = V_{ER} + V_{IC}$

the residual volume, $V_R = V_{FRC} - V_{ER}$

the total lung capacity, $V_{TLC} = V_{IC} + V_{FRC}$

Calibration of the spirometer.—The spirometer was connected with a glass bottle of about five-liter capacity. From a volumetric flask, water at room temperature was added to this bottle in successive portions exactly 0.5 liters in volume, through a water-lock, so that the volume of the spirometer was increased in a step-wise fashion. The kymograph curve obtained in this way shows a rectilinear relationship between the recorded distance which the spirometer bell has moved and the changing volume of the spirometer. This procedure was repeated many times over the period of this investigation and it always gave the same value.

A pen deflection of 1 mm on the kymograph corresponds to a 20.3 ml volume change.

Determination of the fixed volume of the system (V_L).—This was carried out in two ways.

(1) The closed system was filled with a helium mixture of 19–20 vol. per cent in the same manner as described for V_{FRC} determinations in subjects. The initial helium concentration (F_{He}) and the spirometer's volume (V_S) were read. After this, about 0.5 liters of air was added by way of the system's water-lock. When gas equilibrium was reached, both F_{He} and V_S were read again. This was repeated until the F_{He} had decreased to about half of the initial value. Since the volume of helium in the system was constant, it must be true that $(V_L + V_S) \times F_{He} = K$ (a constant). This equation, where V_S and F_{He} are variables, is of the second order. If V_S is placed equal to y and $1/F_{He}$ equal to x one gets the first order equation, $y = K\,x - V_L$. The values obtained show that the katharometer gives comparable values for different F_{He} values. V_L is calculated from the last equation. Fifteen such determinations have given a mean value for V_L of 1.46 liters (range = 1.41–1.58 liters).

(2) A mock V_{FRC} determination was carried out with different-sized glass bottles of known volume (= V_{FRC}) as subjects. In the equation for the calculation of the V_{FRC} the only unknown was V_L, which then could be calculated. Nine such determinations were made, resulting in a mean value for V_L of 1.41 liters (range 1.35–1.53 liters). These calibrations were carried out occasionally in the course of the study and they served not only as calibrations of V_L but also as repeated checks of the whole procedure.

For the calculations of V_{FRC}, a value for the volume of the system (V_L) of 1.43 liters was used. This figure appears to have an uncertainty of about ± 0.05 liters, which gives a possible error of the system of about 25 ml. This systematic error has been regarded as of no practical consequence when the lung volumes obtained in the present study are compared with those of other authors.

The Influence of Training and the Random Error of the Method

As each child was studied twice with an interval of 10–15 minutes between the tests, it has been possible to estimate the influence of adaptation to the experimental procedures on the values obtained. Among the 93 children studied, technically satisfactory double tests were carried out in 89 cases, and it has been possible to calculate the differences between the first and second observations of V_{VC} and its subdivisions. Each particular volume has been examined to see if the differences are related to the magnitude of the mean value of the respective double measurements. As no correlation has been found, absolute rather than percentage differences have been used for further analysis. The mean difference with its mean error has been

TABLE 1

The random error in the method of determining different lung volumes.

	V_{FRC}	V_{ER}	V_R	V_{IC}	V_{VC}
Number of double determinations	89	89	89	89	89
Mean difference ($\bar{d}$), liters	−0.0284	−0.0215	−0.0080	+0.0604	+0.0408
Standard deviation of the differences (σ_d), liters	±0.0831	±0.0807	±0.0869	±0.0904	±0.1079
Error in the mean difference (ε_d), liters	±0.0088	±0.0085	±0.0092	±0.0096	±0.0114
$t = \bar{d}/\varepsilon_d$	3.23	2.52	0.87	6.32	3.58
P	< 0.01	0.02–0.01	> 0.05	< 0.01	< 0.01
Standard deviation in an individual determination (σ_x), liters	±0.0588	±0.0571	±0.0615	±0.0640	±0.0764
Mean of all double determinations ($\bar{x}$), liters	1.44	0.716	0.726	1.885	2.599
Coefficient of variation $(\sigma_x \times 100)/\bar{x}$	±4.1 %	±8.0 %	±8.5 %	±3.4 %	±2.9 %

calculated for each item and has been tested against zero (Table 1). The V_{FRC} and V_{ER} are statistically significantly lower in the second observation than in the first. On the other hand, no significant difference has been shown for V_R. This may be due to the fact that the end-expiratory position is depressed during the second observation, probably from the child's being calmer and having had a certain amount of training. A significant increase of the V_{IC} has been observed in the second test, but this increase is larger than the observed reduction in the V_{ER}, which also indicates an effect of training.

However, these statistically significant mean differences are relatively small; they amount to only 2–3 per cent of the mean values for the lung volumes observed. This relatively large number of double determinations has made it possible to show the effect of the children's adaptation. Standard deviations for the differences are considerably larger (Table 1). It has therefore seemed justifiable in judging each separate case, in practical clinical work, to use the mean volumes of the two successive observations even though there was a certain small training effect.

Even though there was this effect of training, it has seemed permissible to calculate the random error of the method for each separate determination, according to Dahlberg. The random errors obtained in this way, which are also expressed as the coefficients of variation of the mean values for each lung volume in the study series, are somewhat larger than the real random error. However, they give an idea of the method's reliability. As can be seen

in Table 1 the coefficient of variation is not the same for the different item. For V_{FRC} it is ± 4.1 per cent. The largest coefficient of variation is found for V_R (± 8.5 per cent), which is explained by the fact that it is obtained from the difference between two separate lung volumes. Since the mean value of the observations for each lung volume has been used in the clinical judging of the results, the accuracy will be better than the random errors indicate.

Conditions of Study

The investigations were carried out between 8 a.m. and 3 p.m. Some of the children were fasting, while others were not. So-called basal conditions at the time of the determination were not considered necessary. On 20 children examinations were carried out twice on the same day, both fasting in the morning and after a meal and usual activity later in the day. (Duplicate determinations were made each time). The mean difference between the basal and non-basal studies has shown no significant difference from zero.

Results

(*With Statistical Treatment*)

Because there is a wide age range in the material the values observed for the different lung volumes vary a great deal in magnitude (Figs. 4–6). It has long been known that physiologic functions in children, e.g. static lung volumes, are related to the individual's body size. Since a child's growth is a function of age, the static lung volumes have often been correlated with age. Metheny collected from the literature up to 1941 a great many studies of the V_{VC} in different age groups.

As body size varies greatly within the same age group, such different body measurements as height, weight and sitting height generally correlate better than age with different physiologic functions. This is true for lung volumes, and is clearly shown in the plentiful literature about V_{VC} in children and even in the few studies of the other lung volumes (Robinson; Morse *et al.*). If weight or height are used with an exponent of 1 there is no rectilinear relationship with any of the lung volumes determined. Such a relationship is desirable for the statistical treatment of the material, especially in investigations where the age range is wide. If height is used with an exponent of 1 the departure from a rectilinear relationship is particularly great. That the use of height to the third power has been shown to be better is explained by the fact that the correlation factor is then made three-dimensional, like the volume.

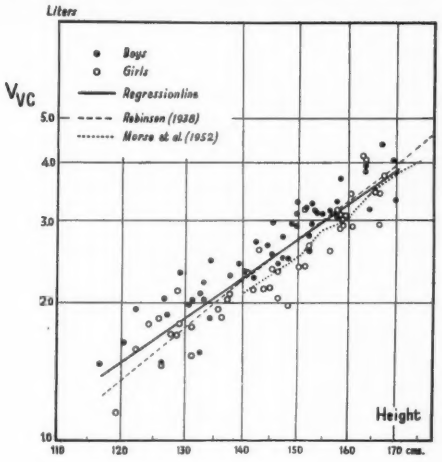

Fig. 4. The vital capacity (V_{VC}) in relation to body height on a double logarithmic plot. The calculated regression line is drawn. The regression lines for the material of Robinson and Morse *et al.* are also shown.

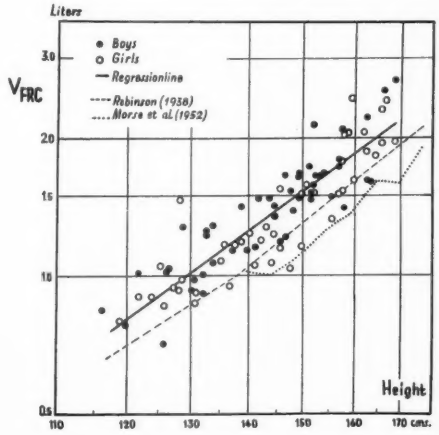

Fig. 5. The functional residual capacity (V_{FRC}) in relation to body height on a double logarithmic plot. The calculated regression line is drawn. The regression lines for the material of Robinson and Morse *et al.* are also shown.

Another body size measurement which is often used is the surface area, which usually is calculated by DuBois's height–weight formula, ($W^{0.425} \times H^{0.725} \times 71.84$). Since this formula was worked out from only ten direct measurements, of which only three were on children, it has seemed very doubtful whether surface area is a useful measurement of the body size for material with a wide age range (Karlberg; Karlberg and Lind).

It has seemed best in calculating the results observed in this study to use the weight, height and sitting height to a power not fixed in advance. The same procedure has been used by Kelly, among others, in his calcula-

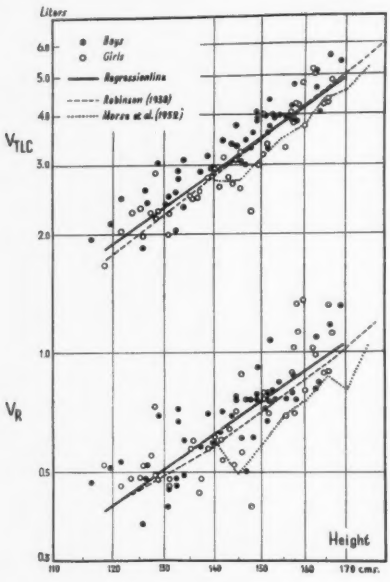

Fig. 6. The total lung capacity (V_{TLC}) and the residual volume (V_R) in relation to body height on a double logarithmic plot. The calculated regression lines are drawn. The regression lines for the material of Robinson and Morse *et al.* are also shown.

tions for a large V_{VC} material. The relationship between the lung volume (y) and the body size (x) can generally be expressed as $y = ax^b + k$, where a, b and k are constants. When the equation is logarithmic, $\log (y-k) = b \log x + \log a$, a rectilinear equation is obtained if k is equal to zero. In order to see if this is the case, the different lung volumes have been plotted out on a double logarithmic scale against the various body measurements. For the relation to body height see Figs. 4–6. As the points on each graph show a rectilinear trend, k must be so small that it can be neglected and set equal to zero. The general equation for the relationship will then be: $\log y = b \log x + \log a$; or, in antilogarithmic terms, $y = ax^b$. The calculation of the regression equation, according to Snedecor, can be made using the logarithms of the variables.

The results of the statistical treatment are given in Table 2. The relationships between the different lung volumes and the three body measurements are given in regression equations along with the residual standard deviations about the regression lines.

In all the graphs the points representing lung volumes for boys and girls are plotted with different symbols. There appears to be a tendency for the values for the girls to be somewhat lower than those for the boys. This difference seems to be so small that it is probably of little practical clinical

TABLE 2

The relationships between different lung volumes and different body measurements expressed in regression equations with the residual standard deviations.

Lung volume liters	Body measurements		
	Weight (kg)	Height (cm)	Sitting height (cm)
V_{FRC} =	$0.0592 \times W^{0.88}$	$0.92 \times 10^{-6} \times H^{2.86}$	$0.211 \times 10^{-5} \times S^{3.09}$
Residual standard deviation around the line	±17.8 %	±15.4 %	±14.8 %
V_R =	$0.0327 \times W^{0.85}$	$1.38 \times 10^{-6} \times H^{2.64}$	$0.206 \times 10^{-5} \times S^{2.94}$
Residual standard deviation around the line	±19.5 %	±19.7 %	±17.8 %
V_{VC}	$0.1127 \times W^{0.87}$	$2.87 \times 10^{-6} \times H^{2.75}$	$0.714 \times 10^{-5} \times S^{2.95}$
Residual standard deviation around the line	±13.8 %	±12.6 %	±12.6 %
V_{TLC}	$0.0862 \times W^{0.86}$	$4.13 \times 10^{-6} \times H^{2.73}$	$0.920 \times 10^{-5} \times S^{2.95}$
Residual standard deviation around the line	±13.1 %	±12.2 %	±11.6 %

importance. When the material is divided into groups of boys and of girls, the resulting groups are not large enough to be treated statistically in great detail. In spite of this the regression equation has been calculated for the separate groups for the height relationship, and from this analysis it was not possible to show any statistically significant difference between the sexes.

The ratios, V_{FRC}/V_{TLC} *and* V_R/V_{TLC}, in adults have been found more useful for judging pathological conditions than the lung volumes alone. Therefore, these ratios have been calculated for this material. Because these are ratios between two lung volumes, variations in body size should influence them less than single lung volumes. As it has been shown in adults that age has an influence on the ratios, we have plotted the values obtained in relation to age in Fig. 7. In this figure the values for boys and girls are marked differently and no tendency towards a sex difference can be seen. Calculation of the linear regression according to age has given the following equations:

$$V_{FRC}/V_{TLC} = 0.00338\,A + 0.393 \quad \text{and} \quad V_R/V_{TLC} = 0.000145\,A + 0.215$$

(A = age in years).

The slope of the fitted line deviates significantly from the horizontal in the first ratio ($P < 0.05$) but not in the second ($P > 0.5$). For this reason, age

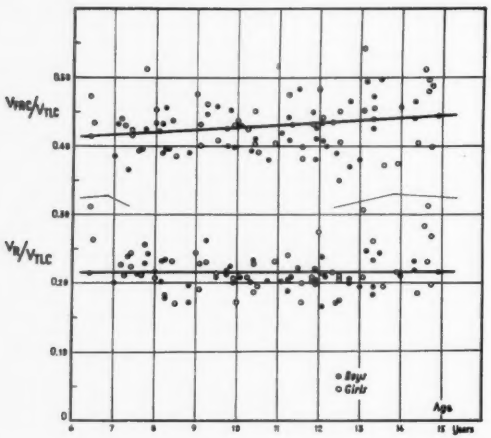

Fig. 7. The ratios of functional residual capacity to total lung capacity (V_{FRC}/V_{TLC}) and residual volume to total lung volume (V_R/V_{TLC}) in relation to age. The regression lines are drawn.

should be taken into consideration for values of the V_{FRC}/V_{TLC} ratio when individual cases are being judged. However, the mean value for V_{FRC}/V_{TLC} varies with age only from 0.417 to 0.440, a change which is small in comparison with the amount of individual variation. Thus, in clinical work, the whole group's mean value with its standard deviation can be used for judging the probability of the V_{FRC}/V_{TLC} being normal in an individual case. This mean equals 0.429 ± 0.0372, while that for V_R/V_{TLC} is 0.217 ± 0.0295. Thus the 95 per cent confidence interval for V_{FRC}/V_{TLC} is 0.355–0.503 and for V_R/V_{TLC}, 0.158–0.276.

Discussion

Table 2 shows the exponents obtained for the different body measurements: for weight, range = 0.85–0.88; for height, range = 2.64–2.86; and for sitting height, range = 2.94–3.09. The exponents for the weight and the height for V_{VC} agree remarkably well with those of Kelly. Morse *et al.*, who tested only whole numbers as exponents, found that 1 for the weight and 3 for the height were best, which also agrees with the above values. That the exponent for sitting height was so high may, at first, seem surprising since in other connections the second power has most often been used. If one considers the great change in body proportions during growth, with a relatively decreasing trunk length, this is not so remarkable.

If the usefulness of the various measurements as correlation factors is judged by the residual standard deviation around the regression line (see Table 2), height seems to be somewhat better than weight. The table shows that the sitting height is even better. However, as the difference is not very pronounced and the standing height is already in general use, there seems

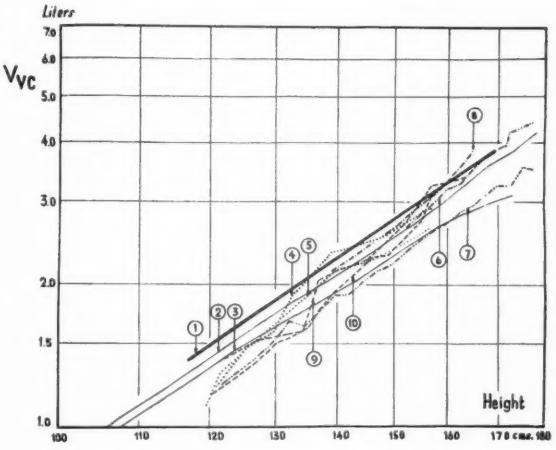

Fig. 8. The vital capacity (V_{VC}) in relation to height on a double logarithmic plot. Results of the present study compared with those of some other authors.
Line 1. Present study, boys and girls.
2. Stewart (1922), boys.
3. Stewart (1922), girls.
4. Serebrowskaja (1929), boys.
5. Serebrowskaja (1929), girls.
6. Kelly (1933), boys.
7. ,, ,, , girls.
8. Schlesinger (1934), boys.
9. Matl and Klimesová (1954), boys.
10. Matl and Klimesová (1954), girls.

to be no reason to change over to sitting height. Since multiple regressions with weight, height, age and index of fat have not improved the correlations to a great extent (Morse *et al.*), calculations of multiple regressions have not been made in this study.

Our results for V_{VC} have been compared with some of the American as well as European studies on large materials (Stewart; Serebrowskaja; Kelly; Schlesinger; Robinson; Morse *et al.*; Matl and Klimesová). This comparison has been made graphically on a double logarithmic plot with height as the correlation factor (Figs. 4 and 8). There is good agreement. For this reason it does not seem to be of such great practical clinical importance to make a statistical comparison between the studies. In the same way, graphical comparisons of V_R, V_{FRC} and V_{TLC} with Robinson's and Morse *et al.*'s materials have been made (Figs. 5–6). As can be seen in Figs. 5 and 6, the present investigation shows higher values for V_R and V_{FRC} than the corresponding ones of Robinson and Morse *et al.* The values for V_{TLC} in this study are also higher, than those of Morse *et al.*, although not so markedly, but agree fairly well with Robinson's. This difference is also seen in mean values of the ratios V_R/V_{TLC} and V_{FRC}/V_{TLC}. Morse *et al.* obtained 0.191 and 0.361, respectively, for these two ratios; Robinson, 0.205 and 0.389. In the present work the ranges of the mean values for the ages studied are 0.216–0.217 and 0.417–0.440, respectively. These latter values have been calculated from the regression equations.

The children in the present study were tested in the sitting position, while

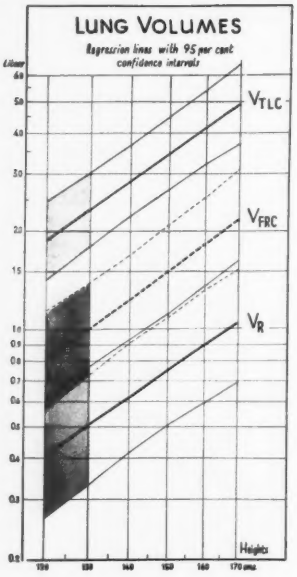

Fig. 9. The present material: Regression lines with 95 per cent confidence intervals for total lung capacity (V_{TLC}), functional residual capacity (V_{FRC}) and residual volume (V_R) in relation to height, on a double logarithmic plot.

Robinson as well as Morse *et al.* studied only recumbent subjects. Since several investigators (Kaltreider *et al.*; Fowler; Whitfield *et al.*) have shown for adults that higher values are obtained in the sitting than in the lying position, the difference in position of the subject in the various studies may well explain the discrepancy of the results.

In this study the material has not been large enough to allow a detailed evaluation of the tendency toward a possible sex difference in the lung volumes as related to body size. Since the possible sex difference is much smaller than the individual variations between the lung volumes and the body measurements it does not seem of practical clinical importance to separate the values for boys and girls.

In judging a possible pathological case on the basis of values obtained with a normal material, such as that presented here, it is generally favorable to use the ratios V_R/V_{TLC} and V_{FRC}/V_{TLC} instead of an individual lung volume in relation to a body measurement. However, in several cases it might be useful to evaluate the separate lung volumes, especially in cases with space decreasing processes in the thorax. To simplify the use of the regression equations found for V_R, V_{FRC} and V_{TLC}, a diagram (Fig. 9) has been constructed where the 95 per cent confidence intervals about the regression lines are also given. These are calculated from the sum of the residual standard devia-

tion about the regression line and the sampling error of the line itself.[1] The volumes are plotted in relation to height and no sex differentiation is made. If the volumes for a subject whose lung function is being studied are plotted on this diagram it is possible to estimate the probability that the actual case belongs to a normal population.

Summary

1. The lung volume relationships in 93 children (50 boys and 43 girls) in the 6–14 year age group were studied.

2. The functional residual capacity (V_{FRC}) was measured by a closed circuit method with helium as the test gas. The method was modified to a certain extent for use in children.

3. The vital capacity (V_{VC}) and its subdivisions, inspiratory capacity (V_{IC}) and expiratory reserve volume (V_{ER}), were determined by spirometry in connection with the determination of the V_{FRC}. The residual volume (V_R) was calculated as the difference between the V_{FRC} and V_{ER}.

4. In 89 double determinations a slight training effect is shown by the fact that the end-expiratory level is somewhat lower in the second determination. This effect of adaptation is so slight, however, that it does not seem to be of any clinical practical importance. Therefore the difference of the double determinations have been used for the calculation of the random error of the method.

5. The relationships between the different lung volumes and weight, height and sitting height have been determined by regression calculations. Of the three measures of body size examined height has proved to be the most favorable when it is raised to a power somewhat smaller than 3.

6. The boys showed a tendency toward having somewhat higher values than the girls but it has not been possible to prove a statistically significant difference.

7. The ratios, V_{FRC}/V_{TLC} and V_R/V_{TLC}, and their relationship to age have been calculated.

8. A diagram for predicting the different lung volumes from height measurements is given.

Etude de la respiration chez l'enfant. I. Volume pulmonaire chez l'enfant de 6 à 14 ans.

Les diverses composantes du volume pulmonaire ont été étudiées dans un groupe de 93 enfants de 6 à 14 ans (50 garçons, 43 filles). Le volume résiduel (*FCR*) a été mesuré par une méthode en circuit fermé, utilisant l'hélium comme gaz témoin. La méthode habituelle a été légèrement modifiée pour son application à l'enfance. La capacité

[1] The estimation of the sampling error of the line itself has been made as follows. Let H_1 be a given value for height. A 95 per cent confidence interval for a certain lung volume (= V_1) corresponding to H_1 can be calculated from the formula

$$V_1 \pm 2\,s\sqrt{\frac{1}{n}+\frac{(H_1-\bar{H})^2}{(S)}}$$

where s is the residual standard deviation; n, the number of cases; and (S), the sum of the squares of the H values around their mean.

vitale et ses composantes (capacité inspiratoire et capacité expiratoire — V_{IC} et V_{ER} dans le texte) ont été mesurées par la spirométrie en association avec la mesure de l'air résiduel (V_{FCR}). V_R a été calculé par la différence entre V_{FCR} et V_{ER}. Un léger effet de l'entrainement a pu être prouvé par une double mesure dans 89 cas; lors de la deuxième épreuve le taux de fin d'inspiration était un peu plus bas. Cependant, cet effet de l'entrainement est si discret, qu'on peut le négliger dans la pratique des épreuves courantes. Pour cette raison, on a pu utiliser la différence entre les doubles mesures pour le calcul des erreurs de la méthode. Les rapports entre les divers volumes pulmonaires d'une part, et le poids, la taille, la taille assise d'autre part, ont été envisagés. La taille a paru l'élément déterminant, à condition qu'elle soit portée à un rapport légèrement inférieur à puissance 3. Il semblerait que le groupe des garcons montre des chiffres un peu plus élevés que celui des filles; mais, on n'a pu apporter néanmoins de différence statistiquement probante. Les rapports V_{FCR}/V_{TLC} et V_R/V_{TLC}, ainsi que leur comparaison avec l'age des sujete ont été étudiés. Un diagramme indique les différents volumes pulmonaires en fonction de la taille.

Atmungsstudien bei Kindern. I. Das Lungenvolumen bei gesunden Kindern im Alter von 6–14 Jahren.

Bei 93 Kindern (50 Knaben und 43 Mädchen) ist das Verhältnis des Lungenvolumens studiert worden. Die funktionelle Residualluft wurde durch einen geschlossenen Kreislauf mit Helium als Testgas gemessen. Die Methode wurde auf eine bestimmte Grösse zum Gebrauch bei Kindern modifiziert. Die Vitalkapazität und ihre Unterteilungen (V_{IC} und V_{ER}) wurden durch Spirometrie in Verbindung mit der Bestimmung von V_{FRC} bestimmt. V_R wurde aus der Differenz zwischen V_{FRC} und V_{ER} berechnet. Bei 89 Doppelbestimmungen zeigte sich ein leichter Trainingseffekt dadurch, dass der Endexspirationsspiegel bei der zweiten Bestimmung etwas tiefer lag. Dieser Adaptationseffekt ist jedoch so leicht, dass er keine praktische klinische Bedeutung zu haben scheint. Deshalb ist die Differenz der Doppelbestimmungen für die Errechnung der Fehlerbreite der Methode benutzt worden. Das Verhältnis zwischen den verschiedenen Lungenvolumen und Gewicht, Höhe und Sitzhöhe ist durch regressive Kalkulation errechnet worden. Von den drei geprüften Körpergrössen hat sich die Höhe als die günstigste erwiesen, wenn sie zu einer Grösse etwas kleiner als 3 erhoben wird. Die Knaben zeigten eine Tendenz, etwas höhere Werte als die Mädchen zu haben, aber es war nicht möglich, eine statistisch bedeutsame Differenz nachzuweisen. Das Verhältnis V_{FRC}/V_{TLC} und V_R/V_{TLC} und seine Beziehung zum Alter sind berechnet worden. Ein Diagramm zur Vorausberechnung der verschiedenen Lungenvolumen aus Höhenmassen wird gegeben.

Estudios respiratorios en la infancia. I. Volumen pulmonar de niños sanos entre 6 y 14 años.

Se estudió la relación del volumen pulmonar en 93 niños (50 varones y 43 mujeres) de 6 a 14 años de edad. La capacidad residual funcional se midió en circuito cerrado usando el método del helio, dicho método fué ligeramente modificado para poderlo aplicar a niños. La capacidad vital y sus modificaciones (V_{IC} y V_{ER}) se determinaron por espirometría efectuandose al mismo tiempo la determinación del V_{FCR}. El V_R fué calculado como la diferencia entre el V_{FCR} y el V_{ER}. En 89 determinaciones dobles el entrenamiento mostró tener una pequena influencia evidenciada por el hecho de que

el nivel expiratorio máximo fué algo mas bajo en la segunda determinación. Este efecto de adaptación es tan pequeño que no parece tener importancia práctica o clínica. La diferencia anotada en determinaciones dobles fué utilizada para calcular el error casual del método. La relación entre los diferentes volúmenes pulmonares y el peso, la estatura y la altura sentado, fué determinada por cálculo de regresión. Del las tres medidas antedichas, la estatura de pié mostró ser la mas favorable cuando su exponente es algo menor de 3. Los varones mostraron una tendencia hacia valores algo mayores que los de las niñas pero fué imposible probar una diferencia estadísticamente significativa. Las relaciones V_{FCR}/V_{TLC} y V_R/V_{TLC} fueron calculadas así como su relación con la edad. Se incluye un diagrama que permite, poseyendo la medida estatural, predecir diferentes volúmenes pulmonares.

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Experimental Approach to the Pathogenesis of Retrolental Fibroplasia

VI. The Influence of the Oxygen Concentration on the Oxygen-Induced Changes in the Mouse Eye

by BO E. HELLSTRÖM

Introduction

In animal experiments previously reported (Gyllensten and Hellström (3, 4, 5)), which dealt with the effect of oxygen exposure on the immature mouse eye, concentrated oxygen was used, i.e., a concentration between 98 and 100 per cent, as analyzed with a Beckman oxygen analyzer. Whereas adult animals succumbed in this atmosphere within a few days, newborn mice displayed a greater tolerance and could survive for several weeks. A high mortality, a slower gain in weight and signs of pulmonary damage indicated, however, that the oxygen had toxic effects other than on the eyes.

A study of the influence of lower oxygen concentrations seemed indicated for many reasons. Firstly it seemed of interest to investigate the oxygen effect in concentrations, where the eyes were more selectively affected, to rule out, for instance, the influence of general hypoxia through pulmonary damage. Secondly it seemed of value to explore the correlation between frequency and intensity of the eye changes on the one hand, and the oxygen concentration on the other. Such information might determine if, with a gradual lowering of the oxygen concentration, the ocular pathology successively decreased or whether a critical level existed, below which the oxygen effect suddenly disappeared. Finally it was felt that if, in the animal experiments, oxygen concentrations were kept at levels commonly used in incubators for premature children, this would increase the practical value of the conclusions.

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Some information was to be gained, however, from studies already reported by other investigators. Ashton *et al.* in experiments with kittens used four levels of oxygen concentrations: 70–80, 45–55, 35–45 and 25–35 per cent and found complete vasoobliteration in the most sensitive age groups with 70–80 per cent, severe with 35–55 per cent and doubtful or absent with 25–35 per cent. The influence of the different levels of oxygen exposure on other retinal structures was not reported, nor was the effect on the vaso-proliferative stage.

Michaelson *et al.* (7), also using the technique with injection of India ink, studied the effect of increased oxygen on the development of the retinal vessels in mice. These experiments suggested that an increase of the oxygen concentration to as low as 40 per cent inhibited, to some extent, the growth of retinal capillaries during the first few days of life. The normal capillary pattern was said to be established within a few days of the return of the animal to normal atmospheric conditions.

Gerschman *et al.*, also reporting lesions in the eyes of newborn mice continuously exposed to oxygen, used concentrations between 65 and 75 per cent.

Patz *et al.* in their original study (8) exposed newborn rats, mice, kittens and puppies to 70–80 per cent oxygen. In more recent reports (9, 10), dealing partly with the influence on the retinas of rats and dogs, the oxygen exposure included concentrations from 40 to 60 per cent. The data are so far only summarized, but it was stated that oxygen concentrations below 40 per cent had no effect on the retinal vessels.

The present study was undertaken with the view of investigating the influence of different concentrations of oxygen in a more systematic and extensive way. It was thought of value to explore the effect of different concentrations also for varying durations. As great experience had been gained from earlier work with mice, this animal was again used with the understanding that the relative immaturity of the eyes of newborn mice, as compared with those of premature children, limited the practical conclusions that might be drawn from the employment of this animal.

Material and Methods

The same strain of black mice (C 57 BL/6) was used as in previous experiments. The feeding and handling of the animals, the types of gas chambers used and the method for oxygen analysis were the same as described in other papers (3, 4, 5). The oxygen concentration was achieved by mixing oxygen and nitrogen in suitable proportions. The range of fluctuations in oxygen concentrations was ± 2 per cent. The flow through each chamber was 0.5 l per minute. CO_2 was not measured. The humidity was close to 100 per cent and the temperature ranged between 20 and 25°C. As distin-

TABLE 1

The distribution of 214 surviving animals.

Oxygen concentration (per cent)	Number of surviving animals		
	5 days in oxygen, followed by 10 days in air	10 days in oxygen	30 days in oxygen
30	10		16
40	10	11	22
50	32	8	15
60	23		13
70	16		14
80	10		14
	101	19	94

guished from previous experiments with concentrated oxygen the mothers of the young mice seemed to tolerate the present lower concentrations well and no interchange was necessary, except for the group exposed to 80 per cent for 30 days. The concentrations of oxygen used were 30, 40, 50, 60, 70 and 80 per cent. At the beginning of the exposure the animals were not older than 16 hours. The duration of the oxygen exposure was either 5 or 30 days and in a small additional group 10 days. Following the short exposure of 5 days, the oxygen was replaced by air within a few minutes and the animals were allowed to stay there for 10 days before preparation. Subsequent to the long exposure for 30 days the animals were immediately killed and prepared. In addition to these main series, two groups of animals were studied immediately following 10 days' exposure to 40 and 50 per cent oxygen respectively, for reasons mentioned below. The histologic technique was in every detail the same as in earlier investigations (3, 4).

Two hundred and fourteen young mice survived the exposure. The distribution of these among the different concentrations and duration of oxygen has been tabulated (Table 1). No special control groups were arranged, as control animals of different ages from the same strain were available from previous experiments.

Results

The mortality rate was on the whole considerably lower than in earlier experiments with exposure to concentrated oxygen and interchange of the mothers and amounted to approximately 25 per cent. It did not seem to increase with higher concentrations of oxygen. The general condition of the surviving animals seemed to be unimpaired and there was no constant trend concerning the gain in weight in relation to the oxygen concentration (Table 2).

TABLE 2

Mean weight of animals exposed to different concentrations of oxygen.

Oxygen concentration (per cent)	Weight in gram	
	5 days in oxygen, followed by 10 days in air	30 days in oxygen
30	6.0	9.4
40	4.1	9.4
50	6.3	9.0
60	6.1	11.6
70	5.9	9.3
80	5.9	6.9

Short exposure.—A very characteristic pattern of eye change is the result of the exposure of newborn mice to *concentrated* oxygen for 5 days, followed by a stay in air for 10 days (3, 4, 5). This includes pathologic changes of the vascular system of the eye and of the structure of the retina. The initial inhibition of the outgrowth of retinal vessels during the stay in oxygen, is followed by a vasoproliferative stage mainly of the vessels in the nerve fibre layer. The extensive changes occur chiefly in the posterior part of the retina, which is thickened, folded, and where especially the nuclear layers are irregular, distorted and intermixed. These irregularities of the retinal structure seldom occur without concomitant proliferations of retinal vessels. In the anterior part of the retina near the ora serrata capillaries are frequently absent, but spindle-shaped cells not forming a capillary lumen are sometimes found in the nerve fibre layer. The nuclear and plexiform layers are usually regular in this part of the retina. In addition, persisting and probably proliferative hyaloid vessels are a constant finding together with hemorrhages in the primary and secondary vitreous body.

This type of eye change occurred in all groups, excepting the one exposed to only 30 per cent oxygen (Fig. 1). The frequency is found in Table 3. From this can be deduced that the incidence is very high with concentrations from 50 per cent and above. Below 50 per cent the frequency rapidly decreases, but still at 40 per cent eye changes are not rare. Asymmetric changes were common with the lower concentrations, whereas the groups exposed to 60 per cent and above, most frequently showed those of a symmetric bilateral nature. As for the intensity of the ocular pathology, changes of the eyes in the group exposed to 40 per cent were classified as slight to moderate, whereas those in the other group varied between slight and

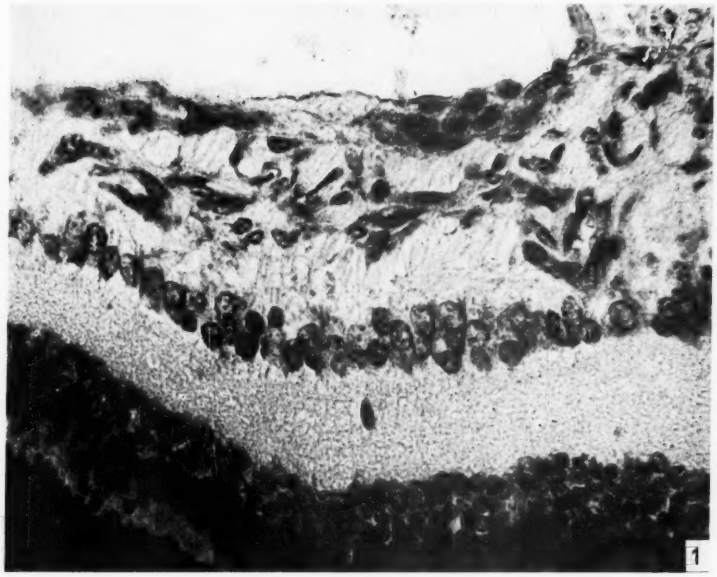

Fig. 1. Animal exposed to 50 per cent oxygen for 5 days followed by 10 days in air. Proliferating vessels in the nerve fibre layer. (× 420)

severe. There was no constant trend indicating an increased severity with increasing concentration during oxygen exposure above 40 per cent. Thus severe changes following a 50 per cent exposure were not infrequent, and only slight changes following an 80 per cent exposure could occur.

TABLE 3

The frequency of eye abnormalities following a short exposure to different concentrations of oxygen (5 days in oxygen, followed by 10 days in air).

Oxygen concentration (per cent)	Number of animals	Number of cases with eye abnormalities	Number of cases with bilateral eye abnormalities
30	10	0	0
40	10	3	1
50	32	21	13
60	23	22	18
70	16	13	11
80	10	10	10

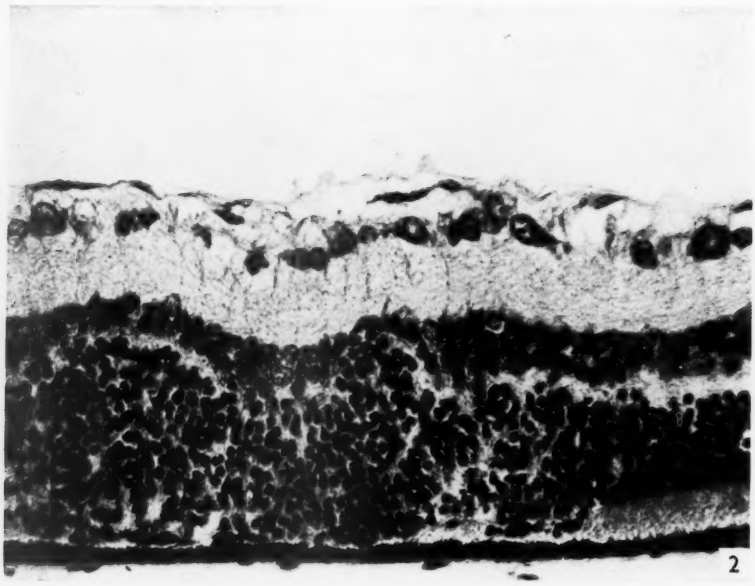

Fig. 2. Animal exposed to 50 per cent oxygen for 30 days. Moderately atrophic changes of inner plexiform and inner nuclear layers with intermixing of nuclear layers and layer of rods and cones. No vessels in the nerve fibre layer. (× 420)

It can be concluded from this part of the investigation that the safe limit for oxygen concentrations harmless to the mouse eye with short exposures, probably lies between 30 and 40 per cent. At 40 per cent and above, the risk for severe eye changes rapidly increases.

Long exposure.—The ocular changes following a prolonged continuous exposure to *concentrated* oxygen are characterized by a completely or partly inhibited vascularization of the retina. Part of the nutrition of the retina seems to have been taken over by proliferating hyaloid vessels, which are often found creeping along the surface of the nerve fibre layer and especially in the papillary region where they form a vascular membrane. Uncanalized clusters of endothelial or mesenchymal cells are not uncommon in the nerve fibre layer, and they probably represent failure of attempts at vascular outgrowth. Atrophic changes with irregularities of the layers are frequent, especially in the middle sector of the retina. In this area the atrophy mainly concerns the inner plexiform, the inner nuclear and outer plexiform layers and frequently leads to a fusion of the nuclear layers. In the same part of the retina the outer nuclear layer and the layer of rods and cones are often

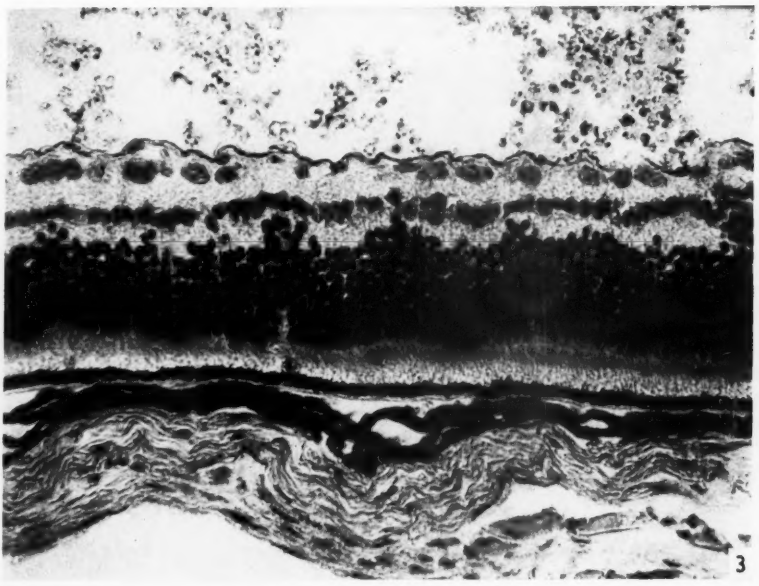

Fig. 3. Animal exposed to 60 per cent oxygen for 30 days. Severely atrophic changes of the inner layers of the retina and complete absence of vessels in the nerve fibre layer. (× 420)

intermixed. In the peripheral sector, including the ora serrata, there sometimes occurs a more general atrophy of less intensity which affects all retinal layers without distortions. Vitreous hemorrhages are common together with delayed disappearance of the primary vitreous body.

This type of eye pathology occurred in all groups exposed for 30 days, with the exception of the one where the oxygen concentration was 30 per cent (Figs. 2 and 3). In the latter group the histologic picture of the eyes was entirely normal (Fig. 4). The occurrence of oxygen-injured eyes in the other groups is found in Table 4. From this is clear that the risk for oxygen injury is still fairly low at 40 per cent, but at higher concentrations it rapidly increases. With increasing concentrations both eyes are as a rule affected.

As for the intensity of the eye changes mentioned, there was an unequivocal correlation between the degree of vascular inhibition and the concentration of oxygen. At 40 per cent this effect was rare and slight, at 50 per cent it was frequent but seldom complete, at 60 and above, it occurred in all cases, at 70 it was frequently complete and the deep capillary layer

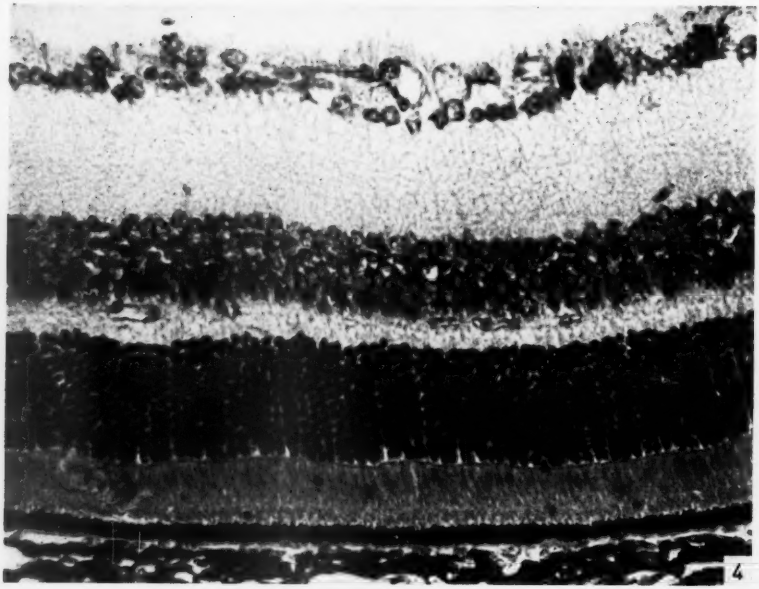

Fig. 4. Animal exposed to 30 per cent oxygen for 30 days. Normal retina. (× 420)

between the inner nuclear and outer plexiform layer was always missing. At 80 per cent there was a complete absence of vessels both in the superficial and deep layer in nearly all cases.

An obvious inverse relationship existed between the occurrence of hyaloid and retinal vessels. The more complete the inhibition of retinal vessels the

TABLE 4

The frequency of eye abnormalities following a 30 days' exposure to different concentrations of oxygen.

Oxygen concentration (per cent)	Number of animals	Number of cases with eye abnormalities	Number of cases with bilateral eye abnormalities
30	16	0	0
40	22	3	1
50	15	14	10
60	13	13	13
70	14	14	12
80	14	14	13

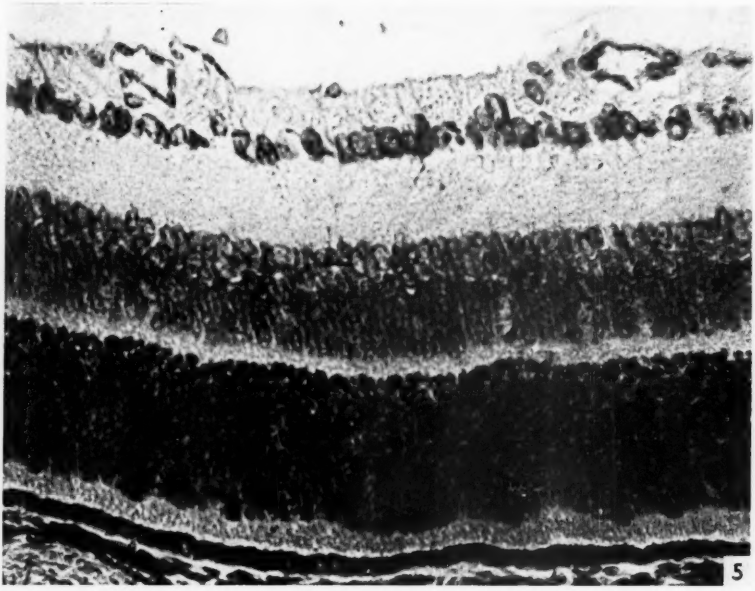

Fig. 5. Animal exposed to 40 per cent oxygen for 10 days. Notice absence of deep capillary net in the retina. Compare with Fig. 6. (× 420)

more intense the proliferation of hyaloid vessels. This fact, together with the observation of anastomoses between the two systems, gave the impression that the hyaloid proliferations are compensatory in nature. This inverse relationship was especially conspicuous in cases with unilateral changes and even in cases with asymmetric changes of one eye, the hyaloid vessels were proliferating only on the side, where the retinal vascular system was inhibited.

There was a close relationship between the incidence of retinal vascular inhibition and atrophic changes. No atrophy was noticed without vascular inhibition and no vascular inhibition without atrophy. On the other hand, in spite of the more advanced inhibition at higher concentrations, there was no obvious increased *intensity* in the atrophic changes with higher concentrations.

A feature not noticed with continuous exposure to concentrated oxygen was the occasional occurrence of localized vascular proliferations in the nerve fibre layer as seen in a few of the cases at these lower concentrations, where the inhibition of retinal vascularization was not complete. Anastomoses between the creeping proliferative hyaloid vessels and vessels in

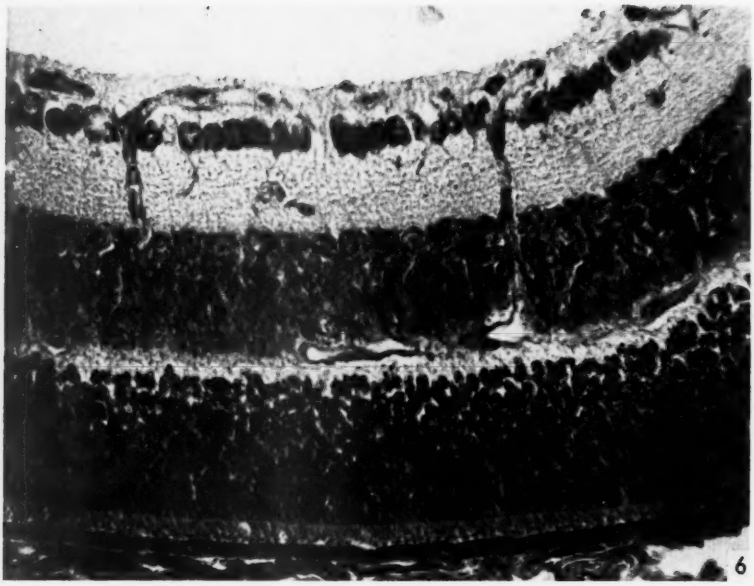

Fig. 6. Control animal, 10 days old. Normally vascularized retina. (× 420)

the nerve fibre layer were not infrequent, and these were sometimes difficult to distinguish from true budding of retinal vessels. On the whole, however, inhibition and probably obliteration of retinal vessels are the dominating features in contrast to the conspicuous and extensive hyperplasia of the retinal vessels during the stay in air, following short oxygen exposures.

In some additional experiments 19 newborn animals were exposed to 40–50 per cent for 10 days without subsequent stay in air. There was a partial or complete inhibition of superficial vessels in the nerve fibre layer in about half of the cases, whereas deep capillaries were completely inhibited in all cases (Figs. 5 and 6). This initial inhibition is overcome in most cases during the more prolonged 30 days' exposure with a continuous 40 per cent oxygen, whereas it persists in most cases of continued exposure to 50 per cent. Other information gained from these additional experiments was the fact that no atrophy had developed up to 10 days, which consequently takes a longer time to develop. Partly for this reason it seems logical to assume that the vascular damage is primary and the atrophic changes are secondary. Also in a few of these cases localized hyperplastic changes of vessels in the nerve fibre layer were occasionally seen (Fig. 7).

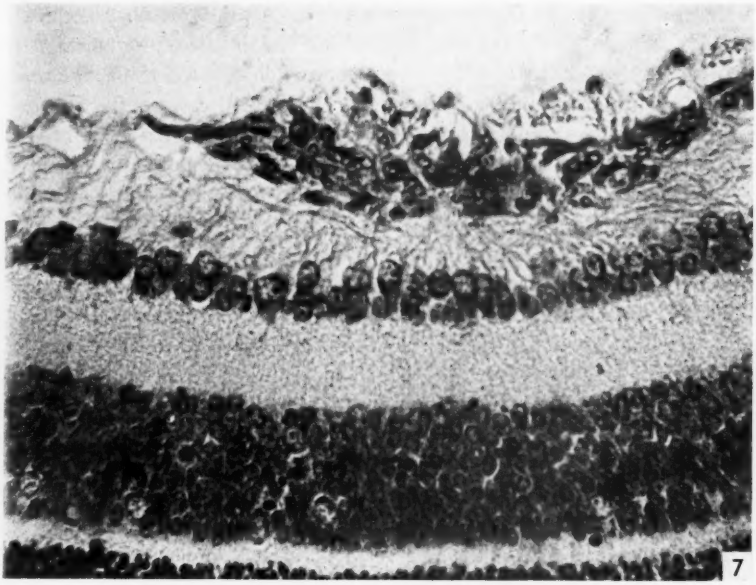

Fig. 7. Animal exposed to 40 per cent oxygen for 10 days. Localized proliferative changes of retinal vessels in the nerve fibre layer. (× 420)

Discussion

The present experiments represent an attempt to investigate the correlation between the oxygen concentration and the oxygen-induced changes of the eyes in newborn mice.

For a relatively short exposure followed by a subsequent stay in air, this mode of treatment induces retinal changes dominated by vasoproliferation. This effect is produced sometimes already with a 40 per cent concentration. The incidence then rapidly increases with higher concentrations, while on the other hand the intensity of the changes is not closely dependent on the oxygen concentration.

Continuous exposure to oxygen causes a partial or complete inhibition of retinal vascularization and constriction and probably obliteration of the vessels that develop. This mechanism initially affects at least the deep capillary net in all cases exposed to 40 per cent or above. A prolonged exposure reveals that the effect at 40 per cent is in most cases only temporary. From 50 per cent and above, the vascular inhibition seems to be permanent at a frequency following the oxygen concentration. This effect is accompanied

by atrophic changes of the retina, and it seems probable to assume that lessened nutrition and oxygenation due to the impaired circulation are the cause. The fact that the severity of atrophy does not follow the increasing vascular inhibition at higher oxygen concentrations, can partly be due to the increased oxygenation of the blood that might compensate the impaired blood supply. The localization of the atrophies to the inner layers of the retina can be explained by the probability that the outer layers are partly supplied by choroid vessels. The atrophic changes are most intense in the middle sector, possibly due to the fact that this area is remote from the extraretinal blood supply, as suggested by Gerschman *et al.*

The greater sensitivity of the deep capillary net to oxygen effect has not been noticed before and it includes also the perpendicular anastomoses from the superficial capillary net. According to Michaelson (6) and others the deep plexus is more associated with the venous part of the circulation and drains into the venules.

Although the vascular changes with continuous exposure are dominated by inhibition of retinal vessels, localized proliferative changes were occasionally noticed in the nerve fibre layer as proliferating endothelial nodules or occasionally as actual capillary tufts. This is in accordance with the results presented by Patz *et al.* (8, 9, 10).

The results of the present study are not in agreement with the findings published by Michaelson *et al.* (7). Their material, however, was small and the structure of the retina was not studied. The value of using an injection technique exclusively in studying these problem seems to be limited.

The results are in good concordance with those reported by Ashton *et al.* concerning the vasoobliterative effect in kittens, which was found to be severe already with 35–55 per cent.

The practical application of the results of the present study to the problem of preventing retrolental fibroplasia is limited mainly by two factors. The first concerns the entirely different outcome of the disease in man and animals. In man the severe end-result is a retrolental membrane formation, in mice atrophic changes dominate. The second limitation lies in the different maturity of retinal vascularization. The premature human retina is far more mature in this respect, than that of a newborn mouse. This does not exclude, however, that the margin between an innocent and a highly injurious concentration is as narrow as in the mouse, although possibly on a higher level.

This view obtains additional, and more direct support in the preliminary report of the co-operative group for the study of retrolental fibroplasia. In this report the average concentration of oxygen to which the infants were exposed during the first nine days was 53 per cent in those cases

developing either active or cicatricial retrolental fibroplasia, whereas the average concentration for those infants whose eyes were normal was 47 per cent, suggesting a critical level, beyond which the risk rises rapidly.

Summary

1) The influence of the oxygen concentration on the oxygen-induced changes of the eyes was studied in 214 newborn mice.

2) A concentration of 30 per cent did not cause any histologically detectable changes. At 40 per cent an injury of the eyes could be demonstrated in relatively few cases. This occurred following both short and long exposures, covering both vasoobliterative and vasoproliferative phase of the oxygen effect. In addition an initial delay in the formation of the deep capillary net of the retina was to be found in all cases.

3) From 50 per cent and above, the incidence of eye injury rapidly increases, and the margin of safety thus seems to be narrow.

4) The significance of these findings with regard to retrolental fibroplasia in premature infants is discussed.

Contribution expérimentale à la pathogénie de la fibroplasie rétrolentale. VI. Influence de la concentration d'oxygène sur les modifications provoquées par l'oxygène sur l'œil de la souris.

L'influence de la concentration d'oxygène sur les modifications provoquées par l'oxygène sur l'œil a été étudiée sur 214 souris venant de naître. Une concentration de 30 % ne provoque aucune modification histologique décelable. A 40 %, une atteinte oculaire est démontrable dans quelques cas seulement. Cette modification suit aussi bien les séjours longs ou courts en atmosphère oxygénée, l'effet néfaste étant aussi bien une vasooblitération qu'une vasoprolifération. En outre, un retard dans l'apparition du réseau capillaire profond de la rétine est observé dans tous les cas. A un taux égal ou supérieur à 50 %, la fréquence de l'atteinte oculaire s'accroit rapidement, et la marge de sécurité semble bien mince lorsqu'on atteint ces chiffres. La signification de ces résultats par rapport à la fibroplasie rétrolentale du prématuré est discutée.

Experimenteller Beitrag zur Pathogenese der retrolentalen Fibroplasie. VI. Der Einfluss der Sauerstoffkonzentration auf die sauerstoffbedingten Veränderungen beim Mäuseauge.

An 214 neugeborenen Mäusen ist der Einfluss der Sauerstoffkonzentration auf die sauerstoffbedingten Veränderungen des Auges untersucht worden. Eine Konzentration von 30 % führte keinerlei histologisch nachweisbare Veränderungen herbei. Bei 40 % konnte bei relativ wenigen Fällen ein Augenschaden demonstriert werden. Dieser lag sowohl nach kurzer wie langer Einwirkung vor und es wurde die vasoobliterative wie auch vasoproliferative Phase des Sauerstoffeffektes erfasst. In allen Fällen wurde zusätzlich eine initiale Verzögerung der Formation des tiefen Kapillarnetzes der Retina gefunden. Von 50 % und darüber nimmt das Vorkommen von Augenschäden rapide zu und die Spanne der Sicherheit scheint eng zu sein. Die Bedeutung dieser Befunde im Hinblick auf die retrolentale Fibroplasie Frühgeborener wird diskutiert.

Intento experimental de aclarar la patogénesis de la fibroplasia retrolental. VI. Influencia de la concentración sobre los cambios producidos por O_2 en los ojos de rata.

Se estudió la influencia de la concentración sobre los cambios producidos por oxígeno en los ojos de 214 ratas recién nacidas. Una concentración del 30 % no provocó cambios detectables. Al 40 % se demostró daño en relativamente pocos casos, ocurriendo estros a continuación de exposiciones breves o prolongadas e incluyendo ambas fases del efecto nocivo del O_2, la vasoobliterativa y la vasoproliferativa. En todos los casos se encontró un retardo en la formación de la red capilar profunda de la retina. Al llegar a concentraciones de 50 % o superiores, la incidencia de daño ocular aumentó rapidamente disminuyendo en consecuencia el margen de seguridad. Se discute la significación de estos hallazgos en relación con la fibroplasia retrolental de los prematuros.

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Infantile Genetic Agranulocytosis (Agranulocytosis infantilis hereditaria)

A New Recessive Lethal Disease in Man

by ROLF KOSTMANN

Summary of Supplement 105.

A new disease of infancy is reported. It has been concluded that this disease constitutes a clinical as well as a genetical entity, and it has been named infantile genetic agranulocytosis.

The main characteristics of this disease are as follows. The onset occurs during early infancy with fever and skin infections manifested as boils and phlegmons. There is a complete or almost complete lack of granulocytes in the peripheral blood. The preparations from bone marrow biopsy or autopsy display a marked retardation or block in the maturation of the myelopoietic cells. Without treatment, the disease runs a short course with lethal outcome. If the infections are treated with antibiotics, the affected children may survive for several months or even years. However, the agranulocytosis and the pathologic changes of the bone marrow remain, and the lethal outcome can only be postponed.

Fourteen children (boys and girls) with this disease, belonging to nine families, are described. For six of them detailed clinical and histological data are reported. The remainder had died before the start of this investigation, and only catamnestic data were available. Two of the six children mentioned above displayed only a temporary agranulocytosis, but the pathological changes of the bone marrow resembled those of the other four children.

Most of the affected children could be referred to a common pedigree by objective genealogic methods. All of them belonged to the same geographical isolate inasmuch as the children were either born there or both parents had ancestors there. Close consanguinity between the parents was established in five of the nine families.

The genetical analysis supports the conclusion that this disease primarily

is caused by a single recessive autosomal gene difference (a simple recessive mutation).

The geographical isolate which was surveyed had a population of 9215 in 1950. The incidence of infantile genetic agranulocytosis among newborns was estimated at 1 in 674 or 0.0015. This should correspond to a gene frequency of approximately 4 per cent and heterozygote frequency of approximately 8 per cent. These latter two estimates, however, are somewhat uncertain due to a small effective population size.

Pathogenetically, infantile genetic agranulocytosis is probably caused by primary changes in the function of the bone marrow. Certain results of experiments with in vitro cultures of bone marrow cells seem to indicate a primary effect of the mutated gene on certain metabolic pathways, possibly of the amino acids.

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Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, October 14, 1955

R Lagercrantz: **Collagen diseases and ulcerative colitis.**

According to a recent theory, ulcerative colitis is supposed to show similarities to the collagen diseases. This would imply a different attitude toward operation (colectomy) which is now being recommended in certain severe cases. As support for this theory it is mentioned that, in cases of ulcerative colitis, the basal membrane of the intestinal mucosa has shown similar changes as in the collagen diseases. Of greater significance is the finding of periarteritis nodosa in the colon and other organs which has recently been reported also by Swedish authors (Ihre, Ivemark). Among a material of 160 cases of ulcrative colitis in children, there were three cases which showed more or less characteristic signs of general collagen disease such as a butterfly rash on the face, but LE cells could not be demonstrated. The occurrence of arthralgias, a high gamma globulin and erythema nodosum with ulcerative colitis speaks for a hypersensitivity reaction as do the good results obtained with treatment with ACTH and cortisone. However, it was not possible to show signs of periarteritis nodosa or another collagen disease at operation in six cases or at necropsy of patients who died. Ulcerative colitis can thus occur as one symptom of a general collagen disease, but most of the cases of ulcerative colitis show no signs of such a disease.

G. Ehrenborg: **Five-year-old boy with telengiactatic skin changes of the face, left hand and legs.**

Nosebleeds during the first years of life. Since the age of two years repeated attacks of hematemesis and melena, on several occasions hemoglobin fell to 30 per cent. Gastro-intestinal series shows rough mucosal pattern with thick mucosal folds. Gastroscopy revealed the bleeding source. Teleangiactatic changes were seen in the antrum and pyloric canal with a sharply demarcated boundary between the pathological and the normal mucosa. Because of the severe blood losses, a Bilroth I gastric resection was performed. At examination nine months postoperatively, he is in good condition. No more hemorrhages have occurred. Pathological examination verfied the diagnosis: Osler's Disease with teleangiactasias in the stomach.

Petter Karlberg, Ruth B. Cherry, Florencio E. Escardó, John Lind and Carl Wegelius: **Method for the study of the respiration in newborns.**

A method to study the respiration in newborns during the first minutes of life is described. The volumes of the newborn's earliest breaths are registered simultaneously

with the related intraesophageal pressure changes and at the same time the aeration of the lungs and the respiratory movements are followed by ciné roentgen. For registering the volumes, a mask is placed over the infant's nose and mouth. This mask is connected by a 35 mm diameter tube to a 60-liter glass bottle where pressure changes caused by the infant's respirations are picked up by an electromanometer. The intraesophageal pressure changes are recorded by a second electromanometer. A 1 mm diameter polyethylene catheter is introduced through the mouth so that its tip is between the upper and middle thirds of the esophagus. For the ciné roentgen a Philips image amplifier, which takes up to 50 pictures per second, is used. After amplification, the signals from the two electromanometers are registered on a 4-channel direct-writing recorder (Elema's mingograph). Small spikes on the fourth channel indicate each roentgen exposure.

The different apparatus can be applied to the infant within a few seconds immediately after delivery before the cord is cut, so that the earliest breath can be recorded.

A preliminary study on nine newborns has been done, showing that this combined technic can be used. It was demonstrated that the compliance of the lungs is very low during the first breath, but that the values found later on during the neonatal period are attained within 5–10 minutes.

H. O. Mossberg: **Comparison between the socio-medical conditions of patients admitted to Samariten Children's Hospital in the years 1943–44 and 1953–54.**

This investigation is intended to find out in what measure the changed working and living conditions have affected the population of a children's hospital. To this effect a series of 1500 patients from 1943–44 is compared with a group of 1004 patients from a period ten years later. The analysis shows that acute medical diseases, purely social conditions, cases for investigation, problems of child rearing and nervous symptoms increased as indication for admission, while feeding problems, prematurity, and tuberculosis have decreased during these ten years. The decline of feeding problems is explained by the prophylactic activities of the infant welfare centers; the drop of tuberculosis cases, however, reflects a real decline of tuberculosis. There were somewhat fewer unmarried mothers during the later period, while the number of divorced and remarried ones had increased significantly. The large number of mothers who work outside the home is also striking. Concurrently a marked increase has taken place in the number of children cared for in day nurseries. The number of so called "key children", i.e. children who have the key to the home and take care of themselves at home while the mother is working, has likewise increased markedly. The living standards have clearly improved; in 1943–44 one room was the most usual dwelling while two and three rooms were most common in 1953–54. Demands have apparently also increased since most families think that their apartments are unsatisfactory in spite of these improvements. This examination has shown how changed social conditions affect the population of a children's hospital.

R. Berfenstam and B. Bille: **Why do mothers stop nursing?**

The investigation is based on an interview of mothers in which it was tried to elicit the factors which imperil nursing. It becomes evident that the greatest risks and most of the factors threatening breast feeding are found during the first few weeks, especially at the time of arrival at home from the hospital, and in the second and third months of the baby's life. Judging from the preliminary results, about one half of the mothers

can, nevertheless, nurse until three months without permanent supplement. A smaller group had to stop nursing earlier because of illness of the mother or the child, and in an about equally large group the cause can be found in the social milieu. In many cases there is a lack of information about the manner of increasing the amount of breast milk when it temporarily decreases somewhat. Discussion with the obstetrician is suggested to provide more intense counselling in the maternity hospital. The mothers should also be helped by the infant welfare centers during the first days after leaving the hospital.

Discussion.—*C. Gyllenswärd* points out that in the 1945 population study (arrangements for maternity care) great weight was attached to supervision of the infants in the newborn nursery. The obstetricians are now generally quite favorably disposed toward this problem. The rooming-in system has been tried in a private maternity home but did not work out well there—*G. v. Sydow* notes that it would often be desirable to have the mothers stay longer in the maternity hospital where a unique opportunity exists to work for good baby care and child rearing—first and foremost for breast feeding. At that time the mothers, especially the primipara mothers, feel a great need for advice. This opportunity is not always used to the fullest extent. In the maternity hospital, the mothers should not only learn how to nurse but also how to take care of the child; they should also have the chance to get answers to questions concerning the child's behavior and care.—*B. Söderling:* Nursery care has always been a problem for preventive child care. The basis of good nursing and of the mother's contact with her child is laid in the postnatal period, particularly in case of the first child. As long as every normal woman is to be admitted to a hospital to deliver her child, big obstetrical departments will be needed. In these the baby care will be submerged among the ordinary acute obstetrical problems. A rooming-in system would therefore be desirable, but our newborn nurseries must then be built with smaller units.—*U. Nordwall:* In Stockholm's Breast Milk Bank we have felt the decrease in nursing. In 1944, 16,000 liters of milk were sent in by 600 mothers, while in 1954 an equal number of mothers brought only 9000 liters. The number of mothers supplying us appears to be constant, consequently the propaganda seems to be effective. It is the mothers' perseverance to deliver milk to the bank which is decreasing. This may be connected with the generally decreased interest in breast feeding. It is also possible that the decreased delivery of breast milk is connected with the improved economic conditions which lessen the interest for an additional income.—*K. Kaijser:* In the maternity departments the babies are kept far away from the mothers, and the contact between mother and child becomes short and superficial. Hence the interest in breast feeding is low. A rooming- in system is therefore proposed. Many mothers are disturbed by this. The room in which the baby is kept should be next to the mother's room. When she then begins to stay up out of bed she herself should be able to take care of her child. When a new maternity unit is to be built, the consulting pediatrician should therefore try to participate in the planning so that mother and child come into closer contact with each other, though the child does not stay in the mother's room.

Phenylpyruvic Oligophrenia (Følling's Disease).

M. d'Avignon: **Clinical Aspects.**—Three cases of this disease are described. The first two are siblings, a four-year-old girl and a three-year-old boy. No hereditary history regarding nervous or mental disease or mental deficiency. When the children were about five months old, the mother noted that their development was retarded. At

the age of 7–8 months, both developed convulsions which periodically were very frequent. The marked mental retardation became more prominent with increasing age. On examination we see two severely retarded children. They do not recognize people, not even their own mother. They have absolutely no ability to concentrate, cannot even play, but use toys only to beat or scratch on or to put into the mouth. They appear not to notice the persons in their environment. They bump against others or each other or against a table or a wall. The third patient is a four-year-old boy. There is an aunt who is somewhat retarded, especially in regard to speech. The boy has two healthy siblings of 5 and 10 years. The mother noted his retarded development quite early. She sought medical advice several times, the first time already at the age or one year. It is not possible to establish any contact with the child during examination. He looks past the observer and never meets the latter's eyes. He does not notice persons or toys, beats his hands against things or beats the object monotonously against the floor in a sterotyped fashion for hours. He cannot talk at all and seems to live in a completely separated world without contact with his surroundings and appears severely retarded. Both boys are blond with light blue eyes, the girl has bright red hair and amber eyes. All three children exude a special odor which reminds one of a stable or rat urine. Gerhard's ferric chloride test gave a green urine. The clinical picture of the illnes was then described in greater detail. Marked EEG changes are seen. The patients were put on a phenylalanine-free diet for two months and the ferric chloride test of the urine became negative and the patients' odor disappeared completely. Accroding to previously described cases, an improvement should have been observed with this diet. This did not occur in our cases. The patients became possibly livelier, but their behavior remained about the same as it was on a normal diet. The EEG changes improved somewhat.

Carl A. Larson: **Genetic Aspects.**—Examination of 6097 mental defectives institutionalized within the South Swedish region of Götaland revealed that 29, or 0.5 %, had phenylketonuria. Out of 4825 defectives born in Götaland, 28, or 0.6 %, had the anomaly, including 3410 uneducable individuals with phenylketonuria in 26 cases, or 0.8 %. First-cousin matings among the parents of individuals with phenylketonuria were observed in 12.5 %. The incidence of carriers of the recessive gene of phenylketonuria was estimated to be 1 % of the total population of Götaland. Twenty-four female carriers, mothers of institutionalized defectives, had an average of 4.5 children.

J. Holmberg, E. Jacobsson and N. Malmberg: **Some viewpoints about the composition of milk for infants.**

J. Holmberg, E. Jacobsson and N. Malmberg: **Clinical experiences with a new infant-adapted milk product.**

A new milk preparation with the name Milkotal is described. On that occasion the need for the addition of vitamins C and D to milk preparations is also discussed.

Discussion.—*A. Wallgren*: Doubted the need for such preparations. Recommended continued use of the usual half milk–half barley water mixtures prepared by the mother in the home with regular milk or, if this was not available, regular dried milk. Criticized the addition of vitamin D to Milkotal; this will be a risk either for overdosage, if the child concurrently gets the customary vitamin D supplement, or for too low a dose when the Milkotal feedings are replaced by other food and Vitamin D is forgotten.—

B. Hamne: Opposes the assertion that a breast fed infant requires some vitamin C addition. Vitamin C is concentrated in the breast milk of nursing mothers and is here about five times higher than in her serum. Unless the mother has a very marked vitamin-C deficiency, such a deficiency can therefore not occur in the infant. With the aim of making Milkotal better adapted to its purpose and more like breast milk, vitamin D has also been added to the product. This would mean that no vitamin D supplement should be necessary with this preparation.

C. Engleson: **Congenital diabetes mellitus.**

Description of a 3-year-old boy who had diabetes mellitus during the newborn period. He was treated for 3 months with insulin and then was completely healthy. The author has reviewed all the cases described in the literature and tried to divide them into groups. He was especially interested in a group of 6 or 7 cases with neonatal diabetes, which, like his case, were cured completely. The patient has no hereditary history for diabetes. He was delivered three weeks after term by outlet forceps because of asphyxia. He showed definite signs of postmaturity. On the 6th day of life, glycosuria was detected. Blood sugar 720 mg %. No ketosis. Maximum glycosuria 13 %. Legal pos. on the 18th day of life. The patient received 200 to 300 g breast milk, plenty of fluid and electrolytes, 4 I.U. of insulin were started on the 19th day. The ketonuria disappeared promptly. The blood sugar fell slowly to about 250 to 300 mg %. After 1 month's therapy, the blood sugar was normal, the glycosuria gone. After 1 ½ months, a short attempt was made to stop the insulin but the blood sugar level rose and the urine again contained reducing substances. The same dose was restarted. Althogether 3 months' treatment which could then be stopped definitely. The patient has since been healthy.

DISCUSSION.—*P. Zetterqvist* describes a similar case. A full-term girl with a birth weight of 2020 g, thin, listless with poor sucking power. Glycosuria up to 7.8 %, hyperglycemia up to 560 mg % but no acetonuria were noted at 11 days of age. Insulin was started at 14 days; optimal clinical effect was attained with 8 IU daily. Continued to develop normally with good general condition; decreasing insulin requirement so that it could be discontinued completely at the age of 6½ months. At 8 months of age she is healthy and examination is not remarkable.—*A. Wallgren:* Should this be called diabetes mellitus? There is no acidosis. Is this not more likely a transitory hyperglycemia with glycosuria, possibly precipitated by a temporary hormonal imbalance in connection with the change from intra- to extra uterine existence.

B. Broman: **The preliminary results of treatment in hemolytic disease of the newborn.**

The material of Rh pos. infants of Rh neg. or Rh-immunized mothers seen during the last years at Karolinska Sjukhuset consisted of 308 cases with 9 deaths (3 %) during the neonatal period. During the last two years 197 such infants were admitted; 2 of them died (1 %). The result of treatment is compared with the reports from other countries. The need for centralization of the care of erythroblastotic infants is emphasized. Every center should take care of at least about fifty Rh-immunized women yearly so that satisfactory experience can be maintained.

DISCUSSION.—*B. Vahlquist:* The results reported by Broman are excellent and valuable. Centralization in the larger university centers should certainly be continued.

A treatment center might possibly also be needed in the northern part of the country. —*F. Karlström:* 25 cases of hemolytic disease of the newborn have been treated at the children's department in Karlstad. Two of these 25 cases have died; in one the mother had suffered from a severe toxemia of pregnancy and the baby was debilitated at birth (1440 g). In the other case, the child died during an attempted exchange transfusion. Necropsy in this case revealed atrophy of the adrenal cortex with absence of lipids. Beside these, 5 Rh-immunized mothers were sent to Stockholm to be delivered there. One of these infants died during parturition. In one case exchange transfusion was performed and the other three did well without exchange transfusion. —*B. Sievert:* In a fairly large maternity unit in northern Sweden, mothers often are admitted without having been Rh-typed. Grouping cannot be finished before delivery, and the report about a possible immunization arrives too late. It would therefore be desirable to have such a center also in northern Sweden.

B. Söderling: **Traumatic brain damage as etiology of certain reading and writing difficulties.**

A seven-year-old girl is described who showed marked reading and writing difficulties following moderate trauma to the left frontal region of the skull. There was no radiological evidence of skull fracture and no disturbance in her general condition or the ability to speak. She reads upside-down writing, writes mirror writing with ther left hand and is generally disoriented. In the sandbox she excutes the most chaotic constructions of upside-down objects and animals. The EEG is moderately pathological with slow activity, but no focal signs. The patient recuperated completely within several months.

Discussion.—*B. Hallgren:* These symptoms agree well with the parietal lobe syndrome of Gerstmann which occurs after damage, e.g. hemorrhage, in the dominant parietal lobe. In this syndrome there is a disturbance of orientation in space which was also present in this case. The main signs are right–left confusion, finger agnosia, ianbility to calculate, and agraphia. Variable additional symptoms often appear, consisting mainly of different derangements in the symbol functions including inability to comprehend speech, to recognize colors or to name them, constructive apraxia and hemianopsia.

N. O. Eriksson: **Obstructive uropathy in children.**

Urinary tract obstructions can, by infection or by increasing the pressure in the renal pelvis, cause changes in renal function. All hydronephroses must be considered to be of mechanical origin until proven otherwise. The aim should be an early diagnosis in order to save as much as possible of the renal parenchyma. The history of the patient is of little help: except for the urinary tract infections, the majority of unilateral hydronephroses are completely asymptomatic. Palpable tumors occur occasionally; pain is quite unusual but does occur as a typical symptom of hydronephrosis caused by obstruction at the uretero-pelvic junction by an anomalous vessel. The urine in these hydronephroses is often sterile. In bilateral hydronephrosis, the main symptom is often a general malaise with gastro-intestinal symptoms such as dyspepsia. This general disturbance diverts the attention from the urinary tract and delays diagnosis. The non-protein nitrogen is often normal and this contributes to a false diagnosis. Tubular function is affected first in an obstruction, and this results in decreased concentrating ability and a tendency to acidosis. The NPN rises only when the patient is dehydrated.

Bilateral hydronephroses are usually found with infra-bladder obstructions, e.g. congenital valves. Difficulties of urination are almost always absent in these cases. The complete obstructions cause death in utero or very soon after delivery. Recurrent urinary tract infections should, in children of all ages but especially in infants, give rise to suspicion of congenital obstruction. Intravenous urography, urethrocystography and cystourethroscopy are recommended for the establishment of a diagnosis since they quickly show the degree and location of the obstruction. The surgical treatment of all types of hydronephrosis should preserve the organs to the greatest extent possible. The choice of operative method is individualized and should take place during the operation. Complete restoration of function cannot always be expected after operation. That which was destroyed preoperatively cannot be replaced and one must sometimes be content to arrest an otherwise progressive destruction of the kidneys. A summary of 12 operated cases of congenital urethral valves was demonstrated.

Discussion.—*L. Garby and H. Ulfendahl:* Conventional methods of estimating kidney function, based upon chemical analysis of blood and urinary components during various imposed conditions, are valid only if the assumption of complete impermeability of the mucosa of the lower urinary tract is made. Consequently, deviations from normal excretory behaviour cannot, in the general case, be ascribed to altered kidney function. It has been shown (Garby and Ulfendahl, *Acta Physiol. Scand.*, in press), that significant changes of the concentration of Na^+, Cl^- and H^+ in the urine occur during passage through the ureters in rabbits. The direction of transmucosal transport is roughly determined by the concentration gradient across the mucosal barrier. Anatomical and physiological considerations make it reasonable to assume that, in patients with obstructive uropathy and hydroureters, these effects are larger than during normal conditions. As a consequence, the following pathophysiological characteristics may be expected in these cases: relative isostenuria and polyuria, increased bicarbonate excretion, diminished excretion of hydrogen ions, metabolic acidosis and a subnormal response to Pitressin injection. These features are almost identical with those actually found in cases of obstructive uropathy, a fact which strongly supports the hypothesis advanced. Conclusive evidence, and an evaluation of accompanying renal dysfunction, should be obtained by comparing bladder urine:pelvic urine concentration ratios in cases of obstructive uropathy with the same ratios in normal subjects. Of course, arguments from data comparing the bladder urine and pyelostomy urine from the same patient are valid only if it is assumed that the two kidneys perform identically.

L. Philipson and E. Tveterås: **The occurrence of C-reactive proteins in the neonatal period.**

C-reactive protein is a protein substance which appears in the serum during the acute infectious diseases and during certain degenerative conditions. It seems to be either a rapid gamma globulin or a slow beta globulin. A comparison between the determinations of C-reactive protein by the capsule swelling method of Löfström and the precipitation thest of McCarty gave essentially corresponding results. The acute phase protein does not appear to pass the placental barrier if the mother's titer is of medium height. In older children, the C-reactive protein behaves essentially as in adults. Our experiences indicate that smaller children have the ability to form such a protein.

DISCUSSION.—*P. Hedlund:* Philipson has noted that the precipitation test gave a higher frequency of positive results when the C-reactive protein content was low. Fifty-two of 376 sera gave different results with Löfström's capsule swelling method and the precipitation test, 47 gave a positive reaction with Löfström's method but negative precipitation reaction. Only 5 sera were positive with the precipitation test and negative with the capsule swelling method. One wonders if it is the same substance that is demonstrated with the different tests. The appearance of acute phase protein was shown, in an investigation of 200 children, mostly under one year of age, to be much more transient than in adults. Experiments with newborn rabbits proved that few-hour old animals produced acute phase protein in the same manner as fully grown ones. It is not clear what the function of the acute phase protein is, nor is it known where it is produced. Even with a large number of experiments with tissue cultures from various organs, the place of formation of the acute phase protein has not been determined.

E. Rabo: **Does triple vaccination give effective protection against pertussis?**

The effectiveness of pertussis vaccination was supposed to be decreased by combination with other vaccines. At the Karlskoga infant welface center, 300 children were registered in 1951–52. They received three subcutaneous injections of the Swedish triple vaccine, which corresponds to a total dose of 60–75 billion bacteria. The vaccination was generally begun between the third and sixth months of life and was completed at intervals between injections of at least one month. Almost the same number of concurrently registered control patients were not vaccinated. When the series was reviewed four years later, all the vaccinated as well as the non-vaccinated controls were found again. (Average observation time: 33 months.) To study the long-term effect the investigation was complemented by a group of 150 children who were vaccinated with an uncombined pertussis vaccine in 1949–1951 together with 135 controls who were followed for five years. All these children have also been found again. Altogether 36 non-vaccinated children had pertussis, and numerous cases continually occur in the control group, while among the vaccinated ones (92 of whom received booster doses) not a single case of pertussis has yet occurred. The author concludes that pertussis vaccination gives good protection for a longer time than previously assumed, and that the Swedish triple vaccine gives equally effective protection as the best uncombined foreign vaccines.

DISCUSSION.—*J. Ström:* An examination of the material from the country's infant welfare centers shows that in Södermanland district 77 % are vaccinated with triple vaccine, in Uppsala 66, Halland 57, Örebro 50, Östergötland, northern Kalmar, Kristianstad and Värmland and Västmanland between 45 and 50 %. Six provinces, on the other hand, show much lower figures. Nevertheless progress seems to be continuing. One of the reasons for the caution advocated by some may be uncertainty about the vaccine's effectiveness—an uncertainty which appears to be completely unjustified in the light of Rabos' investigations. Maybe a certain reticence is based on the fact that pertussis has recently become milder. The children profit from vaccination also by obtaining a basic immunity agaist diphtheria and tetanus. Vaccination will continue to be voluntary.—*B. Vahlquist:* It is now definitely known that the Swedish triple vaccine gives protection against pertussis which is in a class with that offered by the best foreign pertussis vaccines. The long duration of the protection is of special interest. The psychic trauma of vaccination is being reduced by carrying

out the procedure at the early age of 3–6 months and by the addition of xylocaine which eliminates the pain almost immediately after injection—*E. Mannheimer:* The low frequency of triple vaccination in certain areas may be due to the fact that many private physicians carry out such vaccination without reporting this to the Health Department. Complications seem to be more and more unusual.—*P. Hedlund:* A local reaction in the form of a sterile or an infected necrosis at the site of injection is closely tied up with the composition of the vaccine and the size of the dose. The relationship between the protein and aluminium contents is especially significant. Aluminum is added to increase the antigenicity of the vaccine, but it should not exceed a certain amount per dose in relation to the protein content. The higher the protein content of the vaccine, the greater is the risk of necrosis.

Rolf Lundström: **Immune globulin in complications of small pox vaccination.**

At least 400,000 cases of smallpox occur yearly in the world. Intercontinental travel increases the risk of infection; therefore obligatory smallpox vaccination has to be continued in this country. Every year between 60 and 70 patients are admitted to hospitals in Sweden because of complications of smallpox vaccination. The majority are benign and heal rapidly. Death occurred in three cases during a five-year period. For the treatment of such complications, the State Bacteriological Laboratory has immune globulin against vaccinia which is intended for use in vaccinia generalisata, eczema vaccinatum and vaccinia gangrenosa. Ordinary human gamma globulin can, under certain conditions, also be used for such treatment. One child with generalized vaccinia and hypogammaglobulinemia was treated in Kronprinsessan Lovisa Children's Hospital. The patient was given gamma globulin. This gamma globulin was made from blood of military personnel who were revaccinated at their induction. There was thus reason to believe that antibodies against vaccinia virus would be present in fairly large numbers in this gamma globulin.

Discussion.—*L. Silverstolpe* describes a 9-month old girl who was vaccinated correctly and developed a generalized spread of the pustules with high fever. She had about 40 secondary pustules over the entire body. The girl was treated with gamma globulin which also was made from blood of military personnel. Already after two hours, improvement was noted. On the following day the temperature dropped and the rash faded.—*G. v. Sydow* has seen 15 cases of complications in the form of generalized vaccinia and eczema vaccinatum, including one severe case. It is important to try to prevent vaccination complications. The vaccination should be placed so that neither the child nor playmates can reach the site. Instead of vaccinating on the arms, it is wiser to place the vaccination lower down under the clothing and to cover it with a bandage. A child with non-vaccinated siblings in the home should not be vaccinated either. Seven of the 15 complications did not occur in the vaccinated child but in the siblings. This is another reason for promoting early vaccination. If vaccination is performed at about 5–6 months of age, non-vaccinated siblings will become unusual after several years.

G. Tönnberg: **Micromethod for cold agglutination.**

Citrated blood taken with a capillary pipette is used for the titration of cold agglutinins. The titration is done with a modification of the author's earlier described method with the patient's citrated plasma together with unwashed blood cells.

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BOOK REVIEW

Books received.

Books received by *Acta Paediatrica* are acknowledged under this heading. In the interest of the readers, selections will be made for more extensive reviews as space permits.

ANDRE-THOMAS, YVES CHESNI and Mme. ST. ANNE DARGASIES: Examen neurologique du nourrisson. Editions La Vie Médicale. Paris. 1955. Price 450 francs. 45 pages, 95 figs.

SANDELS, STINA: Utvecklingspsykologiska beteendestudier hos barn i åldern 1½–8½ år. Appelbergs Boktryckeri AB. Uppsala. 1956.

PAOLO TOLENTINO: Le epatiti infettive virali con particolare riguardo all'infanzia. Edizioni Minerva Medica. Saluzzo. 1956.

GASTON LAURET: Urologie de l'Enfance. Expansion Scientifique Française. Paris. 1956. Price 3900 francs. 446 pages, 330 figs.

P. G. KISS: Das Koma und seine Behandlung bei Diabetes mellitus im Kindesalter. S. Karger A. G. Basel. 1956. Price 11.90 francs Swiss. 86 pages, 21 figs.

JOHANNES OEHME: Lues Connata. Abhandlungen aus dem Gebiete der praktischen Kinderheilkunde. Bd. 1. Georg Thieme. Leipzig. Price DM 26.—. 114 pages.

Holldack, K., and Wolf, D.: **Atlas und kurzgefasstes Lehrbuch der Phonokardiographie und verwandter Untersuchungsmethoden.**

Georg Thieme Verlag, Stuttgart, 1955. 171 Seiten, 179 Abbildungen, 4°, Ganzleinen, DM 49.50.

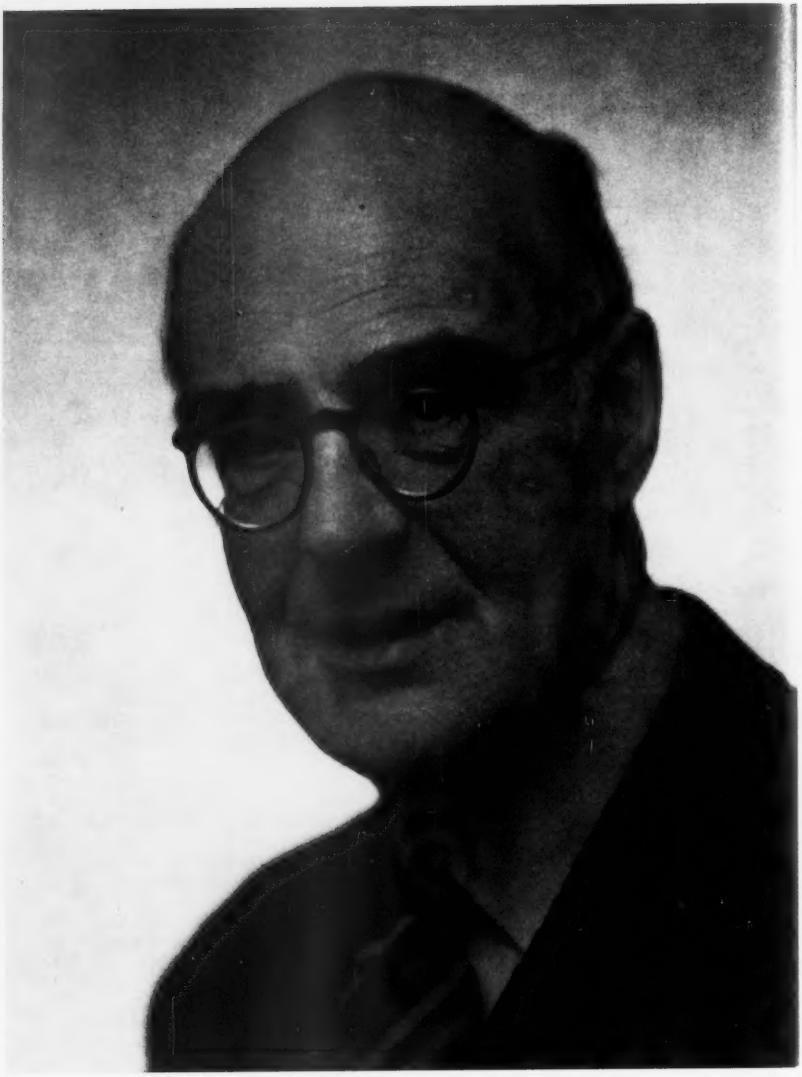
Holldack's and Wolf's phonocardiographic work comprising 171 pages and 149 excellent illustrations can be highly recommended. The authors have used a filter technique which is rather similar to that used in Sweden. By working in a noiseless room the phonocardiograms reproduced have been quite free from external disturbances. The authors have studied phonocardiograms both in normal individuals and in different heart diseases, acquired as well as congenital. The text is easily understood and many informative diagrams are presented. The phonocardiographic literature is followed up to date.

E. Mannheimer
Stockholm

List of Supplements to Acta Pædiatrica.

25. **Schiøtz, Carl,** Eine Darstellung und kritische Bewertung der Ursachen des Rückganges der Säuglingssterblichkeit in Norwegen. Sw. Cr. 5: —.
26. The Proceedings of the Sixth Northern Pediatric Congress, Stockholm August 27—August 29, 1934. Sw. Cr. 5: —.
27. **Rustung, Erling,** Studien über Rachitis. I. Mitteilung. Sw. Cr. 3: —.
28. **Sundal, Alfred,** Chronische infektiöse Erkrankungen der Harnwege im Kindesalter. Sw. Cr. 3: —.
29. **Magnusson, J. Henning,** Zur Kenntnis der Blutveränderungen bei Frühgeborenen. Sw. Cr. 5: —.
30. **Herlitz, C. W.,** Studien über den Krankheitsverlauf und die Therapie des Diabetes mellitus bei Kindern. **Söderling, B.,** Behandlung der Zuckerkrankheit im Kindesalter ohne Diäteinschränkungen. Sw. Cr. 5: —.
31. **Ström, Justus,** Periodisches Erbrechen mit Ketonämie bei Kindern. Sw. Cr. 5: —.
32. **Faxén, Nils,** The Red Blood Picture in Healthy Infants. Sw. Cr. 5: —.
33. **Herlitz, Gillis,** Studien über die Prognose der okkulten Kindertuberkulose. Eine Nachuntersuchung bei tuberkulinpositiven und tuberkulinnegativen Kindern. Sw. Cr. 5: —.
34. **Sällström, Thor,** Die akute Nierenentzündung und ihre Prognose bei Scharlacherkrankungen. **Leeuw, K. De,** The Prognosis of Nephritis in Children. Sw. Cr. 5: —.
35. **Lindquist, Nils,** Studien über die cutane Capillarresistenz im Kindesalter. Sw. Cr. 5: —.
36. **Lange, Cornelia de,** Studien über angeborene Lähmungen bzw. angeborene Hypotonie. Sw. Cr. 3: —.
37. **Forssell, P.,** Klinische und histologische Untersuchungen über die sog. Hexenmilchsekretion. Sw. Cr. 3: —.
38. **Söderling, Bertil,** Zur Früh- und Spätprognose der Säuglings- und Kleinkindertuberkulose, zugleich eine Studie über die Epituberkulose (Eliasberg-Neuland). Sw. Cr. 5: —.
39. **Soveri, Vuokku,** Der Verlauf der Luft durch den Verdauungskanal des Säuglings. Sw. Cr. 3: —.
40. **Selander, Per,** Epidemischer und sporadischer Ikterus. Sw. Cr. 5: —.
41. **Salomonsen, Leif,** Morbus hemorrhagicus neonatorum. Sw. Cr. 3: —.
42. **Leppo, Varpu,** Über den Einfluss der Rübe (Brassica Rapa) auf die Azidität des Harns und des Stuhls bei gesunden und magendarmkranken Säuglingen und Kindern. Ein Beitrag zur Rohkost bei Kindern. Sw. Cr. 3: —.
43. **Brander, T.,** Contents 8 Different Articles. Sw. Cr. 3: —.
47. **Vahlquist, Bo C:son,** Das Serumeisen. Eine pädiatrisch-klinische und experimentelle Studie. Sw. Cr. 10: —.
48. **Wilton, Åke,** Gewebsbiologische Studien über die Pathogenese der Addison-Biermer'schen Anämie. Sw. Cr. 5: —.
49. **Herlitz, Gillis,** Studien über die sog. initialen Fieberkrämpfe bei Kindern. Sw. Cr. 5: —.
50. **Wåhlin, Olof S.,** Über die Methodik bei der Ausführung der Tuberkulinreaktionen sowie über die Verbreitung der Tuberkulinallergie bei Schulkindern im nördlichen Schweden (Västerbotten). Eine statistische Analyse. Sw. Cr. 5: —.
51. **Brandberg, Olof,** Studien über das klinische Bild der Leukosen und der sog. leukämoiden Reaktionen im Kindesalter. Sw. Cr. 5: —.
52. **Edgren, Gunnar,** Prognose und Erblichkeitsmomente bei Eczema infantum. Sw. Cr. 5: —
53. **Roos, Bertil,** Über die Karies des Milchgebisses bei Kleinkinder. Mit besonderer Berücksichtigung der Bedeutung einiger sozialer und medizinischer Faktoren. Eine sozialmedizinische Studie aus Südschweden. Sw. Cr. 5: —.

54. **Broman, Birger,** The Blood Factor Rh in Man. A Clinico-serological Investigation with Special Regard to Morbus Haemolyticus Neonatorum (»Erythroblastosis foetalis»). Sw. Cr. 5: —.
55. **Peltsara, Heikki,** Tierexperimentelle Rachitisuntersuchungen mit besonderer Berücksichtigung der Muskeltätigkeit. Sw. Cr. 5: —.
56. **Rinvik, Roald,** BCG-Vaccination in Children, The effectivity and some immune biological manifestations. Sw. Cr. 5: —.
64. **Landtman, Bernhard,** Heart Arrhythmias in Children. Sw. Cr. 3: 50.
65. The Proceedings of the Eighth Northern Pediatric Congress. Helsingfors June 27—June 29, 1946. Sw. Cr. 5: —.
66. **Mossberg, Hans-Olof,** Obesity in Children. A clinical-prognostical investigation. Sw. Cr. 5: —.
67. **Ahvenainen, E. K.,** On Changes in Dilatation and Signs of Aspiration in Fetal and Neonatal Lungs. Sw. Cr. 5: —.
68. **Wegelius, Ruth,** On the Changes in the Peripheral Blood Picture of the Newborn Infant immediately after Birth. Sw. Cr. 5: —.
71. **Maasik, Elisabeth,** Über die Einwirkung der Kälte auf das periphere Blutbild des Säuglings. Experimentelle Untersuchungen. Sw. Cr. 5: —.
72. **Otila, Eino,** Studies on the Cerebrospinal Fluid in Premature Infants. Sw. Cr. 5: —.
76. **Lewis-Jonsson, Johannes,** Chorea. Its Nomenclature, Etiology, and Epidemiology in a Clinical Material from Malmöhus County 1910—1944. Sw. Cr. 5: —.
77. The Proceedings of the Ninth Northern Pediatric Congress, Copenhagen August 13—August 16, 1948. Edited by **Paul Drucker.** Sw. Cr. 5: —.
79. **Wasz-Höckert, Ole,** The Tuberculin Reaction in Different Parts of the Skin and the Sensitivity in Rheumatoid Arthritis. With special reference to the technical error in the Matoux reaction. Sw. Cr. 5: —.
80. **Frisell, Erik,** Studies on Bacterium Bifidum in Healthy Infants. A clinical Bacteriological Investigation. Sw. Cr. 5: —.
81. **Tähkä, Hilkka,** On the Weight and Structure of the Adrenal Glands and the Factors Affecting Them, in Children of 0—2 Years. Sw. Cr. 5: —.
83. The Proceedings of the Tenth Northern Pediatric Congress Stockholm June 13—June 16, 1951. Edited by **Justus Ström.** Sw. Cr. 10: —.
84. **Simell, Greta,** Über das Menarchealter in Finnland sowie einige speziellen Beobachtungen über damit verbundene Faktoren. Sw. Cr. 15: —.
86. **Lindquist, Bertil,** Effect of Vitamin D on the Metabolism of Radiocalcium in Rachitic Rats. Sw. Cr. 15: —.
87. **Berfenstam, Ragnar,** Studies on Blood Zinc. A Clinical and Experimental Investigation into the Zinc Content of Plasma and Blood Corpuscles with Special Reference to Infancy. Sw. Cr. 15: —.
89. **Karlberg, Petter,** Determination of Standard Energy Metabolism (Basal Metabolism) in Normal Infants. Sw. Cr. 15: —.
91. **Levander-Lindgren, Maj,** Electrocardiografic Studies in Scarlet Fever. An Investigation with Special Reference to the Effect of Penicillin Treatment. Sw. Cr. 15: —.
92. **Tunevall, Gösta,** Oto-Rhinological Infections in Childhood. Sw. Cr. 5: —.
95. **Nilsby, Ivar,** Non-Bacterial Meningo-Encephalitides in Children. Sw. Cr. 15: —.
97. **Engleson, Gunnar,** Studies in Diabetes Mellitus. Sw. Cr. 15: —.
101. **Enell, Herbert,** BCG-Vaccination, Tuberculin Allergy and Tuberculosis in School Children. Sw. Cr. 15: —.
102. **Rafstedt, Sture,** Studies on Serum Lipids and Lipoproteins in Infancy and Childhood. Sw. Cr. 10: —.
103. The Proceedings of the Eleventh Northern Pediatric Congress, Oslo June 28—July 1, 1954. Edited by **Arne Njå.** Sw. Cr. 15: —.
104. **Ivemark, Björn I.,** Implications of Agenesis of the Spleen on the Pathogenesis of Cono-Truncus Anomalies in Childhood. Sw. Cr. 10: —.
105. **Kostmann, Rolf,** Infantile Genetic Agranulocytosis (Agranulocytosis infantilis hereditaria). Sw. Cr. 10: —.
106. **Larsson, Yngve,** Morphology of the Pancreas and Glucose Tolerance in Biliary Fistula, in Common Bile Duct Obstruction and After Ligation of Pancreatic Duct. Sw. Cr. 20: —.



Carl Andersen

IN HONOUR OF

CARL FRIDERICHSEN

ON HIS SEVENTIETH BIRTHDAY

JUNE 5, 1956

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Carl Friderichsen

Carl Friderichsen was born in Copenhagen on June 5th 1886, and took his medical degree at the age of 26. In 1923 he became a doctor of medicine, and in 1933 was appointed Senior Physician of the Pediatric Ward of Sundby Hospital, Copenhagen.

Friderichsen acquired a thorough theoretical training at the Pathological-Anatomical Institute of Copenhagen University and at the Pharmaceutical Institute, and then became for two years Assistant Physician at the University Medical Clinic (Ward A) before being appointed Assistant Physician at the Queen Louise Children's Hospital in 1919.

Whilst serving as a young doctor in the Pediatric Ward of the Rigshospital, he published in 1918 the work that has most contributed to make known his name in the scientific world: "Nebennierenapoplexie bei kleinen Kindern". Here Friderichsen described on the basis of his own cases and cases from medical literature the pathological picture which, at the proposal of Glanzmann in 1933, is now generally referred to as the Waterhouse-Friderichsen syndrome. He discussed comprehensively the aetiology and pathogenesis of the symptoms, and suggested that intoxication and infection might be the causes; the correctness of this theory was confirmed after a number of years.

Thirty-six years later Friderichsen was invited to review the Waterhouse-Friderichsen syndrome at the First International Endocrinological Congress held in Copenhagen 1954, where he had the satisfaction of being able to furnish a comprehensive description of the therapy.

Friderichsen's scientific ability and interests have been the driving force of his life as a pediatrician. His doctor's thesis, "Concerning acidosis in the case of infants", was of high quality, as worthy of perusal now as it was when written 35 years ago. A large series of works has come from Friderichsen's hand, all on important subjects, and treated in an original and critical manner. As examples may be mentioned the well-known works: Tetany in a suckling with latent osteitis fibrosa in the mother, from 1938, Sulfa shock treatment of pneumonia, from 1941, and the Investigation concerning the prognosis for febrile convulsions, from 1954.

Friderichsen has played a great and important role in Scandinavian pediatric cooperation. Since 1918 he has directed the "Scandinavian Pediatrical Literature Circle", and thanks to his interest in the pediatricians of the

Nordic countries and their work, he has greatly contributed to understanding and scientific exchanges in the North. He was the obvious president when the 9th Nordic Congress of Pediatrics was held in Copenhagen in 1948.

At the meetings of the Danish Pediatric Society Friderichsen has always been a faithful attendant, and his interest and enthusiasm has enriched many a discussion. He was chairman of that society from 1928 until 1934.

In his practical medical work Friderichsen has evinced eminent qualities on a par with his scientific attainments. In addition to his hospital he has coped with a large practice, and rightly enjoys a high reputation in this sphere. It was felt fitting that he was entrusted with the medical care of the children of the King and Queen of Denmark.

There are many reasons why colleagues, collaborators and friends have wished to mark Carl Friderichsen's 70th birthday by this commemorative document. We feel the urge to acclaim him for his eminent scientific work, and to thank him for good and loyal cooperation, for his excellent and inspiring guidance of the ward and in the Pediatric Society, and for his friendship.

PREBEN PLUM

Publications by Carl Friderichsen

1. Die quantitative Bestimmung der Salizylsäure im Blute und deren Wirkungen auf das Herz. *Archiv für exper. Pathologie u. Pharmakologie, 80:* 235, 1917.
2. Mineralstoffernes Relation til Ernæringsforstyrrelserne hos det spæde Barn. *Ugeskr. f. Læger, 12:* 446, 1917.
3. Demonstration af en "Piebald". *Ugeskr. f. Læger, 34:* 1421, 1917.
4. Nebennierenapoplexie bei kleinen Kindern. *Jahrbuch f. Kinderheilk. u. Physische Erziehung, 87.* der dritten Folge 37. Bd., Heft 2 (1918), p. 110.
5. Myasthenia gravis pseudoparalytica. *Ugeskr. f. Læger, 36:* 1430, 1919.
6. Om Virkningen af store Jerndoser. *Ugeskr. f. Læger, 11:* 500, 1919.
7. Undersøgelser over Acidosen hos Spædbørn. *Forhdl. ved Første Nordiske Kongres for Pædiatri,* 1939, 1919.
8. Første Nordiske Kongres for Pædiatri i København 1919 (Referat). *Ugeskr. f. Læger, 36:* 1418, 1919.
9. Et Tilfælde af congenit Ødem. *Ugeskr. f. Læger, 37:* 1185, 1920.
10. Et Tilfælde af Myotonia congenita. *Ugeskr. f. Læger, 38:* 1215, 1920.
11. Anden Nordiske Kongres for Pædiatri i Stockholm 1921 (Referat). *Ugeskr. f. Læger, 28:* 932, 1921.
12. Om Neutralitetsregulationen hos Brystbarnet. *Medicinsk Revue,* Februar 1923, p. 21.
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The Diagnostic and Prognostic Value of the Initial Electroencephalogram in Children with Convulsions[1]

by F. AASS, B. R. KAADA and K. H. TORP

Convulsive seizures in infants and children are always dramatic events whether they occur in the course of another disease or whether they have no apparent cause. Most parents automatically call for the physician who often refers the patient to the hospital. In Oslo most of these patients are admitted to the Pediatric Department at Ullevål Hospital for further examination.

This department was opened 5 years ago, and it was decided it would be interesting to analyse the material of convulsive disorders in children during this period. It was of special interest to establish *the diagnostic and prognostic value of the initial electroencephalogram (EEG) obtained in children within a few weeks after they had their first convulsive seizure.* Furthermore, the purpose has been to study the prognostic value of other observations made during the first stay in hospital. This problem is of primary concern for the parents of these children.

Material and Results

During the five-year period, from July 1st, 1950 to July 1st, 1955, a total of 182 children younger than twelve years were admitted for convulsive seizures, i.e. 4.9 per cent of all the children admitted to the Pediatric Department during the same period. Convulsions are a rather heterogeneous sign. For the patient and his family, however, all convulsions appear as an entity, and in this paper the problem is considered from this point of view. Therefore, all children who presented localized or generalized tonic or clonic convulsions have been included.

All figures refer to observations made during the first stay in hospital. Four of the 182 children, however, had previously been in other hospitals for convulsions.

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TABLE 1

Normal EEG		90
Abnormal EEG		
Epileptiform discharges	focal	38
	generalized	38
Other abnormalities		16
Total, abnormal EEG's		92
Total, all EEG's		182

Observations during the First Stay in Hospital

The EEG was always taken several days or weeks after the first convulsive seizure. As pointed out by Bridge (1949, p. 269) abnormalities in a single record taken within a few hours of the episode may be present that indicate only temporary postconvulsive changes. These usually disappear in less than 24 hours.

EEG records were obtained in all of the 182 children. In 93 patients the routine EEG (with the patient awake) appeared normal. Sleep-records were obtained in about one third (32) of these children during the first examination and three of these revealed abnormalities of suspect epileptiform character. There was therefore a total of 90 children suffering from convulsions who had a normal EEG (Table 1).

Abnormal tracings, most of which showed epileptiform discharges, were obtained in 92 patients (Table 1). In the following, however, a distinction has only been made between (1) normal and (2) abnormal EEG's and attempts based upon this simplified classification have been made to establish the practical value of the *first* EEG-examination.

Besides EEG, the following examinations were performed in nearly all the patients: cranial roentgenography, ophtalmoscopy, determination of blood sugar (fasting or in connection with seizures), serum calcium and phosphorus, and other supplementary examinations indicated by the clinical picture. In 50 patients pheumo-encephalography was carried out.

The *age* of the children at the onset of the first seizure is presented in Fig. 1. It may be seen that in most cases (70 per cent) the first convulsive seizure occurred during the first three years of life. Seizures were progressively less frequent during later years of childhood.

In each group the proportion of normal and abnormal EEG's obtained within 5–14 days after the first seizure is indicated by white and black columns respectively (see Fig. 1). Only 35 per cent of the children who had their first convulsions before they were 4 years old (127 patients) showed

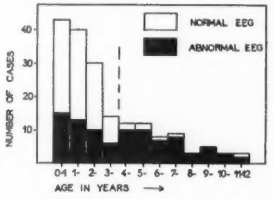

Fig. 1. Age distribution of 182 children at the first onset of convulsions, i.e. at the time of examination.

abnormal EEG's. On the other hand, abnormal tracings were obtained in 87 per cent of those who had their first convulsions after their 4th year (55 patients).

Fig. 2 demonstrates *the relation between the first convulsive seizure and the onset of high fever* (more than 38.5°C = 101.3°F). A distinction has been made between children with a normal EEG (upper part of the figure) and those showing an abnormal EEG-tracing (lower part of the figure). The hatched area within each column indicates the number of children at a certain age who had their initial convulsions during the onset of fever. The total number of such patients was 58 (31.9 per cent of all the children). This figure is consistent with that published by Peterman (1946) who found that 33.4 per cent of the seizures in children were due to or precipitated by fever. It may be seen that "febrile convulsions" occurred in both groups but more frequently in the children with normal EEG's. Seventy-four per cent of all children with febrile convulsions had a normal EEG. This figure is about the same as those published previously by Lennox (1949) and Bjerglund & Brandt (1954) who found 71 and 75 per cent respectively.

In 11 patients the convulsions appeared in connection with crying and breath-holding. In 9 of these cases the onset of the "breath-holding spells" occurred before they were 18 months old. These 9 infants represent a clinical entity in the sense that they suffered from recurrent spells for several months and had normal EEG's in repeated examinations.

The results of the EEG's were correlated with clinical, roentgenological and pathologic-anatomical observations. Organic (cerebral) disorders, which may have been the cause of the convulsions, were found in 24 of the 182 patients. The diagnoses in these 24 children were as follows: cerebral palsy (4), cerebral palsy with hydrocephalus (5), hydrocephalus (4), intracranial haemorrhage (2), meningitis (2), demyelinating encephalopathy (Krabbe) (2), brain injury (1), congenital malformation of the skull (1), aplasia of the corpus callosum (1), the Sturge-Weber syndrome (1), and hypoparathyroidism (1). Abnormal EEG's were obtained in 23 of these 24 patients, thus demonstrating a definite correlation between the EEG-recordings and the abnormal conditions just listed. The only patient with a normal EEG was

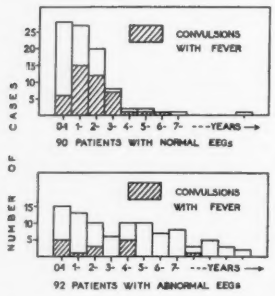

Fig. 2. The relation betweent the initial convulsive seizure and the onset of high fever. Upper part: Age distribution of 90 children with a normal EEG. Lower part: Age distribution of 92 children with an abnormal EEG. The hatched area indicates the number of children who had convulsions during high fever.

a 2½-year-old boy who suffered from cerebral palsy. The EEG of this child was classified as normal. It was noted, however, that it showed some inconstant, slow activity of suspected abnormal nature over the left temporal region.

Follow-up Examinations

In order to assess the prognostic value of the first EEG-examination, attempts were made to contact all patients who had been more than two years under observation after the initial seizure (125 patients). Contact was made with 107 of these patients (85 per cent). The results of the follow-up study are presented in Fig. 3. Again a distinction has been made between the children with a normal EEG-tracing (46 cases, upper part of the figure) and those with an abnormal EEG (61 patients, lower half of the figure) at the first examination. It may be concluded:

1) Of the 46 patients with a *normal* EEG after the first seizure 12 (26 per cent) had recurrent convulsions within 2–5 years (average observation time 3 years). Seven infants with breath-holding spells are included in this figure (dotted part of the columns). If these cases are excluded, convulsions recurred in only 5 of 39 children (13 per cent) with normal EEG's (hatched part of the columns).

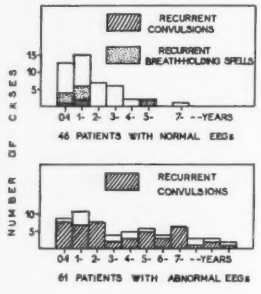

Fig. 3. Follow-up studies. Convulsions (hatched areas) which recurred within 2–5 years after the initial seizure in children with a normal EEG (upper part) and in children with EEG-abnormalities at the first examination (lower part).

2) As many as 46 of the 61 patients with an *abnormal* EEG at the first examination (75 per cent) suffered from recurrent convulsions within 2–5 years (average observation time 3.3 years).

Only in rare instances were children with a normal EEG treated by anticonvulsants after the first seizure, whereas 80 per cent of the children with an abnormal EEG received anticonvulsant drugs after the first attack. The significant difference in the incidence of seizure recurrence between the two groups might therefore have been even more marked if prophylactic treatment had been carried out to an equal degree in both groups during the observation time.

In the selected group of 58 children who had their first seizure during a febrile illness, 33 had been under observation for from 2–5 years. Convulsions recurred in 11 of these patients. Three of them (all with a normal EEG) had one single recurrent attack only, whereas the other 8 (25 per cent), all with an abnormal EEG, had a history of several recurrent convulsions *without* fever. This percentage would probably have been somewhat higher if the observation time had been longer.

Discussion and Conclusions

It should be emphasized that the purpose of the present study has been to assess the prognosis from observations made in connection with the *first* convulsive seizure in infants and children. A careful history, especially with regard to difficulties during the delivery or to perinatal asphyxia, may be of great value, but cannot be appraised objectively by a retrospect study of a selected material. These data have therefore been excluded. Due to the relatively short period of observation, only a short time prognosis can be considered.

From the data presented the following conclusions seem justified:

1) *A history of high fever during the first convulsive seizure* is of little help in evaluating the prognosis. Seizures during fever may mean "simple febrile convulsions" (in the present material with an observation time of 2–5 years 75 per cent). In about 25 per cent, however, there were recurrent, non-febrile seizures associated with abnormal EEG's. These figures are somewhat lower than those published by Peterman (1950), who in a series of 128 children with febrile convulsions, observed recurring convulsions without fever in 40 per cent and recurring convulsions only with fever in 29 per cent. On the other hand, our figures are higher than those observed by Thom (1942). In a group of 34 children who were originally classified as febrile convulsions, only one patient had become an epileptic, 6 were mentally retarded and 5 others were seriously defective.

2) *The first EEG* seems to be of considerable value for the prognosis, as

also stressed by Lennox (1949), Bridge (1949) and Peterman (1946, 1950). The tendency to recurrent attacks was in our material about three times greater in children with an abnormal EEG than in those with a normal record (75 and 26 per cent respectively). If the infants with recurrent breath-holding spells, which form a distinct and characteristic clinical entity, are excluded from the latter group, convulsions recurred (often with an abnormal EEG) in only 13 per cent of the children with an initial normal EEG-record (as compared to 75 per cent in children with an initial abnormal tracing). This figure is somewhat higher than that observed by Lennox (1949). In her material convulsions recurred within a three year period in 17 to 50 per cent of the children with abnormal EEG's at the first examination; the figure depended on the type of EEG abnormalities.

It should also be noted that an abnormal EEG was obtained in 23 out of a total of 24 children who had an organic cerebral disease which could be demonstrated by other methods. An abnormal EEG, obtained several days or weeks after the first convulsions, therefore seems to be a fairly reliable criterion for brain damage. Consequently, an abnormal EEG in a child suffering from convulsions strongly suggests that the seizure is due to organic cerebral damage, and that it very often is epileptic in nature. These children should therefore receive anti-epileptic treatment for some time.

3) *The age* at the first onset of convulsions, considered by itself, is of some prognostic assistance. Thus, the incidence of recurrent convulsions was nearly twice as high when the initial attack occurred after the age of four years (Fig. 3). This observation must be seen in relation to the higher frequency of abnormal EEG's in the group of the older children (Fig. 1) and to the higher incidence of simple febrile convulsions before the age of four years (Fig. 2). These observations are consistent with those published by Peterman (1946), Bridge (1949), and others, who from follow-up studies of children with convulsions concluded that epilepsy was diagnosed more frequently as age advanced. Epilepsy becomes the major cause of convulsions between the ages of 3 and 10 years (Peterman 1946). According to the same author recurrent convulsions are usually due to epilepsy.

From these data it therefore seems justified, from a practical point of view, to consider the occurrence of a first seizure *after the age of four years* as an indication of brain damage, even when an EEG has not been obtained. Faced with a child of this category, the physician should prescribe anticonvulsants (assuming that other organic disorders are excluded) until an EEG-record may be obtained. "No study of convulsions is complete without this aid" (Peterman 1950).

If, on the other hand, the onset of convulsions occurs *before the age of four years*, the prognosis is less serious. At this younger age, however, the

EEG-examination seems to be a very helpful criterion in assessing the possibility of seizure recurrence in each individual case. In most cases a normal EEG at this age indicates a favourable prognosis (at least for the first 2–5 years), whereas an abnormal EEG (whether the abnormalities consist of epileptiform discharges or slighter, uncharacteristic abnormalities) indicates far greater possibility for recurrent seizures. It should be emphasized however, that the EEG after the initial seizure may be normal and later on reveal definite abnormalities of epileptogenic nature.

Summary

1) Information about the prognostic value of a single electroencephalogram (EEG) obtained in connection with the first convulsive seizure in infants and children has been obtained from a follow-up study of 182 patients. A single standard EEG, considered by itself, is of unestimable prognostic assistance. An abnormal EEG greatly increases the likelihood that recurrent convulsions will develop.

2) Seizures recurred twice as frequently in children who had their first convulsion after their fourth year as in those who had their first attack before that age.

3) A history of fever during the initial convulsive seizure is of limited value in assessing the prognosis.

Valeur diagnostique et pronostique du premier électroencéphalogramme réalisé chez l'enfant présentant des convulsions.

Les données concernant la valeur pronostique d'un simple électroencéphalogramme (EEG), enregistré au cours de la première attaque convulsive, chez des nourrissons ou des enfants, ont été l'objet d'une étude suivie chez 182 malades. Le simple enregistrement EEG standard s'est montré d'un secours inestimable pour le pronostic ultérieur. Ainsi, un tracé EEG anormal augmente sensiblement la probabilité de nouvelles crises convulsives.

Les crises se sont renouvelées deux fois plus souvent chez les enfants dont le paroxysme initial était survenu après l'âge de 4 ans, que chez ceux dont l'âge lors du premier symptôme était en dessous de ce chiffre.

L'existence de fièvre, lors du premier épisode convulsif semble un signe de bien peu de valeur dans la détermination du pronostic lointain.

Der diagnostische und prognostische Wert des Initial-Elektroencephalogrammes bei Krampfkindern.

Erfahrungen über den prognostischen Wert eines Einzel-Elektroencephalogrammes (EEG), das im Zusammenhang mit dem ersten Krampfanfall bei Säuglingen und Kindern aufgenommen wurde, werden durch ein Studium des Krankheitsverlaufes von 182 Patienten erhalten. Für sich allein betrachtet ist ein einzelnes Standard-EEG nur von untergeordnetem prognostischen Wert. Ein abnormes EEG erhöht jedoch die Wahrscheinlichkeit, dass weiterhin Krämpfe auftreten werden. Wiederkehrende Anfälle treten bei Kindern, die ihre ersten Krampferscheinungen nach dem 4. Lebensjahr hatten, doppelt so oft auf als bei solchen, die ihre ersten Anfälle vor diesem Alter hatten. Die Fieberanamnese während der initialen Krampfanfälle ist von beschränktem Wert für die Prognosestellung.

Valor diagnóstico y pronóstico del EEG initial en niños con convulsiones.

Se analiza el valor de un solo EEG obtenido con motivo del primer ataque convulsivo en 182 lactantes y niños. Un EEG standard y único es de una inestimable ayuda pronóstica. Un EEG anormal aumenta las posibilidades de convulsiones posteriores. La frecuencia de un segundo ataque convulsivo fué doble en los menores que habían tenido su primer episodio después del cuarto año de edad comparado a los que lo habían sufrido a edad mas temprana. Una historia de fiebre acompañando al primer ataque es de limitado valor cuando se analiza el pronóstico.

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From the Queen Louise Hospital for Children, Copenhagen (Chief: Professor Oluf Andersen, M.D.)

Sarcoidosis (Boeck) in a Child Treated with Cortisone and ACTH

by HENNING ANDERSEN

Sarcoidosis is rare in children. Among the 1700 cases collected from the literature by Schmid only 5% were children. The same applies to e.g. Gravesen's series of 150 Danish patients. The great majority of the children have ranged in age from 10 to 15 years.

A detailed description of the nature and clinical features of this disease is not within the scope of this brief report, but the interested reader is referred to Gilg's thesis.

In the course of time numerous forms of treatment have been suggested, but none has had absolutely convincing effect.

Since 1950 cortisone and ACTH have been tried in the treatment of this disease. The rationale of this treatment is still a debated point, and the results have not been consistent. According to recent analyses dealing chiefly with adult patients (Carstensen, Israel *et al.*, Gilg), the treatment is in many cases successful at the outset, but often the improvement is not maintained. The best results have been obtained with the extrapulmonary manifestations as well as in fresh cases of pulmonary sarcoidosis—especially the disseminated variety. On the other hand, pulmonary fibrosis and hilar adenopathy give little or no response.

In addition to the ordinary side effects, administration of ACTH and cortisone involves the risk of explosive and fatal activation of overlooked or erroneously diagnosed tuberculosis or mycotic infection (Israel *et al.*). To the author's knowledge, flare-up of tuberculosis has not been observed during cortisone therapy in cases where the diagnosis of sarcoidosis has been correct.

In view of the meagre experience with ACTH and cortisone in the treatment of sarcoidosis in children, the following case may be of interest.

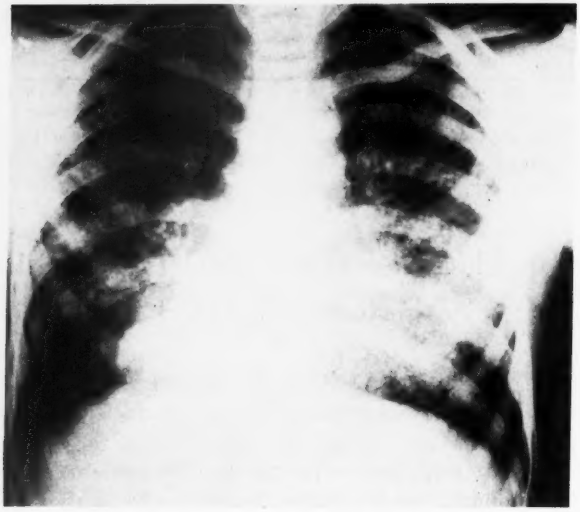

Fig. 1. Pulmonary lesions immediately before treatment.

Case Report

E. B. H., Queen Louise Children's Hospital, case rec. 993/54. A boy, aged 11, whose family history, birth, and postnatal development were not contributory.

Since the age of 2 the patient had been suffering from reccurrent upper respiratory infections. One year prior to admission he had uncomplicated "pneumonia" treated at home with penicillin.

In August 1954 the patient applied to the Finsen Institute, Pediatric Out-patient Department, with enlargement of the cervical lymph nodes of a few months' duration. As the E.S.R. was elevated and chest radiography indicated sarcoidosis, the patient was admitted to the Queen Louise Children's Hospital on Aug. 21, 1954.

On admission his general health was good and the temperature normal. Auscultation revealed fine, moist râles over both basal lung fields. Moreover, there was generalized, soft swelling of the lymph nodes and moderate splenomegaly. On the left forearm and in the right parietal region a few flat, firm subcutaneous infiltrations, 1 × 1 cm.

X-rays of the lungs revealed numeorus well-defined lesions, up to the size of vermicelli, diffusely scattered in both lungs. X-rays of the skull, hands and feet, vertebral column, stomach, colon, and urinary tract showed no abnormalities.

Biopsy from an inguinal lymph node as well as from the infiltrate on the forearm showed the typical appearance of sarcoidosis.

E.S.R. on admission 42 mm/hour. Hb. 90 %.

W.B.C. 5400—with a normal distribution on differential count.

Moro and Mantoux tests positive (BCG vaccination in 1951).

Histoplasmin, coccidoidin, and ornithosis tests negative.

In the course of the next 6 weeks severe progression occurred, the patient becoming almost moribund, suffering from severe dyspnoea, precordial and abdominal oppression. He also had anorexia, nausea, and vomiting with severe dehydration. At the same

Fig. 2. Lungs after a follow-up of 15 months, 5 months after discontinuation of the treatment.

time he developed iridocyclitis. During this entire period he ran a low-grade fever. The E.S.R. gradually increased to 80 mm/hour and the Hb. fell to 75 %.

At this juncture treatment with ACTH, 25 mg 4 times daily, was initiated. The result was a prompt, dramatic improvement. The nausea and vomiting ceased, the dyspnoea improved, and the conjunctivitis disappeared. At the end of 5 days ACTH was replaced by cortisone, 25 mg 4 times daily by mouth. The improvement was maintained, and the treatment was continued for the next 10 months with decreasing doses of cortisone interrupted approximately every 3 weeks by a few days of ACTH therapy.

After 6 weeks' treatment the patient could be discharged in good health for continued out-patient treatment and control. Two months later he went back to school, where he has been a full-time pupil ever since. The splenomegaly disappeared after a few months' treatment, the lymphadenopathy subsided perceptibly, and the auscultatory findings in the lungs were normal. The subcutaneous infiltrations disappeared at the end of 2–3 months, and the sedimentation rate was also normalized in a couple of months.

Chest radiography showed unequivocal regression of the lesions after two weeks' treatment. After six months' treatment only a few fibrous strands remained in the right basal field, and in another two months the appearance was normal. Biopsy from a lymph node after 8 months' treatment, however, still showed sarcoidosis. At the end of 10 months the treatment was discontinued. There had been no side effects apart from slight moon-face in the first months.

At follow-up in January 1954, 5 months after the treatment was discontinued, the patient was still feeling perfectly well. X-rays of the lungs and bones showed no abnormalities. E.S.R. 7 mm/hour. Hb. 105 %. Skin and eyes normal. A few, rather firm, indolent lymph nodes on the neck and in the axillae. Out of regard to the latter finding and to the last lymph-node biopsy, treatment with Meticorten, 5 mg daily, has recently been instituted.

Discussions

In this case the diagnosis of sarcoidosis (Boeck) seems to be beyond doub
The improvement occurred parallel with the treatment. Of course it i
always difficult to assess the value of therapy in a disease which, like th
present one, has a tendency for spontaneous healing. Nevertheless, it seem
reasonable to assume that the improvement was due to the treatment, a
the more so as previous experience with pulmonary sarcoidosis of this ver
type is to the same effect.

At present it is impossible to make any statement about the long-tern
prognosis.

Summary

An 11-year-old boy developed fulminant sarcoidosis (Boeck) in less than 6 months. He had severe pulmonary lesions, generalized enlargement of the lymph nodes, and subcutaneous infiltrates. ACTH and cortisone therapy, which resulted in prompt improvement, was continued for 10 months. After 15 months' follow-up the boy does not exhibit any signs of the disease, but a lymph-node biopsy obtained 8 months after discontinuation of the treatment still showed sarcoidosis.

Sarcoïdose de Boeck chez un enfant, traitée par la Cortisone et l'ACTH.

Une sarcoïdose de Boeck s'est developpée d'une manière suraiguë, en moins de six mois, chez un garçon de 11 ans. Il existait des lésions pulmonaires importantes, une augmentation diffuse des ganglions lymphatiques, et des infiltrations sous-cutanées. Un traitement par la cortisone et l'ACTH amenait une amélioration rapide. Il fut poursuivi pendant 10 mois. Après un recul de 15 mois, l'enfant ne présentait plus aucun signe de la maladie; cependant, une biopsie ganglionnaire faite huit mois après l'arrêt du traitement révélait encore l'existence de la sarcoïdose.

Cortison- und ACTH-Behandlung bei einem Kind mit Sarkoid (Boeck).

Bei einem 11 Jahre alten Jungen entwickelte sich in weniger als 6 Monaten ein ausgedehntes Sarkoid (Boeck). Er hatte schwere pulmonale Veränderungen, generalisierte Lymphknotenschwellungen und subkutane Infiltrate. Die ACTH- und Cortisontherapie, die eine schlagartige Besserung der Erscheinungen zur Folge hatte, wurde 10 Monate lang fortgesetzt. Nach 15monatiger weiterer Beobachtung weist der Junge bisher keinerlei Zeichen der Erkrankung auf, aber eine Lymphknotenuntersuchung, die 8 Monate nach Unterbrechung der Behandlung vorgenommen wurde, zeigte weiterhin das Bild eines Sarkoids.

Un caso de sarcoidosis de Boeck tratado con ACTH y cortisona.

Un niño de 11 anos desarrolló una sarcoidosis de Boeck severa en menos de seis meses presentando severas lesiones pulmonares, linfadenitis generalizada e infiltrados subcutáneos. El tratamiento con ACTH y cortisona mostró rapida mejoría y fue continuado durante seis meses. Un control a los 15 meses no mostró ningún signo de enfermedad pero una biopsia ganglionar obtenida 8 meses después de suspendido el tratamiento evidenció sarcoidosis.

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Childhood Pneumonia, Including Pertussis Pneumonia, and Bronchiectasis

A Follow-up Study of 151 Patients

by AXEL BIERING

During recent years different authors have tried to estimate the frequency of bronchiectasis as a complication in bronchial asthma and in primary pulmonary tuberculosis.

Finke examined a group of 176 children with "frequent and prolonged respiratory illness, more than half" (of them) "had been affected by pneumonia, or what probably was pneumonia"—"Bronchographic studies in 18 children revealed definite bronchiectasis in 7 and doubtful bronchiectasis in 8". From several studies of patients with bronchiectasis it appears that a great number of patients contract the disease in childhood and particularly in infancy. Among the causative factors pneumonia and pertussis rank highest (Field; Lindskog & Hubbel).

Lees made a roentgenologic study of 150 patients with pertussis. Their lungs were X-rayed once a week. Six patients had almost total collapse of one or more lobes. Four of these patients were studied with repeated bronchographies, which revealed bronchodilatation in the affected lobes. In three the dilatation was transient, but in one it seemed to be permanent. In this patient the atelectasis was complicated by pneumonia.

No other attempts have been made to estimate the actual risk of developing bronchiectasis in pertussis or pneumonia in infancy and childhood.

Materials and Results

Two groups of patients have been questioned and examined 9 or more years after their acute illness.

1. The first part of the material consists of 85 patients who were treated for pneumonia at the childrens department of Sundby Hospital during the year 1938. At the time of admission 23 were less than 1 year old. The diagnoses were confirmed by X-ray pictures in all cases. All the patients an-

[1] With the kind permission of Professor Oluf Andersen, M.D., and Professor Preben Plum, M.D., some of the examinations have been carried out in the Queen Louise Children's Hospital and in the pediatric out-patient clinic of the Rigshospital, Copenhagen.

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swered the questionaire concerning the eventual development of chronic bronchopulmonary disease. Fifty-eight answers gave no reason to suspect such disease. In 27 cases physical examination was found indicated, and 26 of these were examined. Their histories were further detailed and contained evidence of repeated infections of the respiratory tract; in most of the cases these infections were most pronounced during the first years after the pneumonia. Some of the patients had been subjected to adenoidectomy and/or tonsillectomy with good results. Three of the patients had asthma. No case presented evidence of progressing pulmonary disease or symptoms characteristic of bronchiectasis. The patients were submitted to a thorough physical examination. Hemoglobin and E.S.R. were examined. X-ray pictures of the chest in two projections were taken. In no case was any clinical, stethoscopic or roentgenologic sign of bronchiectasis discovered, and hence bronchography was not indicated.

2. The second part of the material consists of patients with pertussis treated in the Blegdam Hospital in 1938 and 1939. There was a total of 708 admissions. The case records have been scrutinized, and the 66 cases in which stethoscopic symptoms of pneumonia or bronchitis were recorded have been selected. Only eight patients had their lungs X-rayed during the disease. Four patients could not be traced. The remaining 62 patients have answered the questionaire. Sixteen of these were less than one year old at the time of admission. Forty-six of the answers did not indicate the presence of pulmonary disease; sixteen answers necessitated further questioning and examination. Fifteen patients were examined, twelve of them in the same way as the patients in the Sundby material. In eleven of these patients neither clinical, stethoscopic nor roentgenologic findings suggested bronchiectasis.

The 12th patient presented a history of repeated febrile attacks with coughing, dyspnoea, pains behind the sternum and profuse mucous expectoration. These symptoms began after the pertussis. Physical examination did not reveal anything abnormal. Stethoscopy was normal, and there was no clubbing of the nails. A chest roentgenogram showed doubtful coarse meshed structure near the base of the right lung, corresponding to the site of the pertussis pneumonia. A bronchogram of the right lung, however, did not reveal anything abnormal.

The 13th and the 14th patient were examined in their homes in other parts of the country. The result of the examinations did not offer particular indication for a roentgen examination of the chest.

The 15th patient developed bronchiectasis:

Case No. 198–38, 271–38, 409–39 and 451–50. Girl, born Nov. 16, 1937, birth weight 2500 g. One month old admitted to another hospital for congenital pyloric stenosis; medical treatment. No pulmonary symptoms during the first year. Nov. 11, 1938 ad-

mitted to the Blegdam Hospital for pertussis. Weight on admission 9550 g, only few and mild attacks, no fever. Stethoscopy: Numerous rhonchi and a few coarse and medium râles over both lungs. Hb. 91 %. Treatment: Pertussis vaccine. Discharged Nov. 19. Readmitted Nov. 23 with an extensive basal pneumonia on the left side and a more circumscript one on the right. Temp. 40.3°C, normal after 2 days. Treatment: Steam. Almost no coughing after Dec. 1. Discharged Dec. 29. Stethoscopy normal. After discharge she continued to cough now and then, and she developed a poor appetite and vomiting. During a third admission of half a years duration (Feb.–Aug. 1939), she had pneumonia at least twice and almost constant stethoscopic signs of bronchitis as well as a bilateral otitis media, complicated with mastoiditis. In the following eleven years she had almost constant cough. She did not expectorate. She had numerous febrile attacks and two or three times she was admitted to different hospitals for pneumonia. Jan. 20, 1950 she was finally readmitted to the Blegdam Hospital. She was in a rather poor condition with chronic dyspnoea and clubbing of the nails, and roentgenograms of the thorax showed a coarse meshed structure in the basal parts of both lungs. Bronchograms showed cylindrical and sacculated bronchiectases in both lower lobes and in the lingula. She was transferred to a department of thoracic surgery where she has been submitted to several operations with extensive lung resections. She still has bronchiectasis in the remaining lung tissue and is severely disabled.

Conclusion

The actual risk of the development of bronchiectasis in childhood after pneumonia and pertussis does not seem to be of any appreciable magnitude. The case history, however, makes it clear that a greater alertness of the medical profession toward the problem of bronchiectasis is desirable.

Summary

By a follow-up study of 151 patients suffering from pneumonia or pertussis-pneumonia one case of bronchiectasis was found.

Pneumonie de l'enfance (y compris la pneumocoqueluche) et bronchiectasie.

L'étude suivie de 151 malades ayant présenté une pneumonie, ou une coqueluche avec pneumonie, n'a permis de déceler qu'un seul cas de bronchiectasie.

Kindliche Pneumonie, einschliesslich Pertussis-Pneumonie und Bronchiektasie.

Bei Nachuntersuchung von 151 Patienten, die an Pneumonie oder Pertussis-Pneumonie gelitten hatten, wurde ein Fall von Bronchiektasie gefunden.

Bronquiectasias y neumonias en la infancia, incluyendo la coqueluchosa.

151 pacientes fueron examinados después de haber sufrido neumonia o coqueluche neumonia, encontrándose bronquiectasias en solo 1 caso.

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Children Born out of Wedlock in Copenhagen, Their Family Milieu at the Age of Five Years

by AGNETE BRÆSTRUP

In Denmark one child out of ten is, fairly constantly, born out of wedlock (ch.o.w.), the total number rising and falling with the total nativity. Besides, 40 % of children born in wedlock (ch.i.w.) arrive before the parents have been married for 9 months. Thus the milieu is not planned for a child at the time of conception of every other first-born baby.

Although 2051 illegitimate children were born in Copenhagen 1947, the total number of unmarried mothers with children under 15 years of age was only about 2300. So a considerable decrease takes place through marriage and adoption. How changeable the living conditions for ch.o.w. are until the family relations have been settled is unknown, but some publications indicate that these children are in a less favourable position, both regarding state of health and mental development, than ch.i.w.

Ch.o.w. are more often premature. Blegen finds that in Oslo 1930–39 12.8 % ch.o.w. were premature, against 6.1 % ch.i.w. Nørregaard finds a corresponding tendency for Copenhagen and considers this a consequence of failure of illegal termination of the pregnancy.

Ch.o.w. are more often still-born. In Copenhagen in 1947 2.6 % of ch.o.w. were still-born and 1.9 % of ch.i.w. Among prematures Nørregaard finds 17 % of ch.o.w. and 13 % of ch.i.w. still-born.

Infant mortality rate is essentially higher. In Copenhagen in 1947: 5.2 % for ch.o.w. against 3.6 % for ch.i.w. At the ages from 1–5 years the mortality seems also to be greater for ch.o.w. (see below).

It must be presumed that greater mortality for ch.o.w. is preceded by a greater morbidity. Certainly the hospitalisation frequency for ch.o.w. is twice as great as the average, but other circumstances may contribute to this; thus ch.o.w. are often accepted at hospital wards because they cannot be nursed and looked after at home.

School education is worse. In the public schools of Copenhagen 60 % of all children are fit for the secondary school which terminates with an examination. This also applies to children of widows, against only 40 % of ch.o.w.

Removal from the home is more frequent. On the initiative of the Juvenile Court of Copenhagen, during 1947–1952 1 child out of every 700 was removed when the parents were living together, against 1 child out of 80, when the mother was single.

From the existing data it must be concluded that ch.o.w. have a less favourable milieu than ch.i.w.: they are more often born prematurely, have a greater mortality and morbidity, profit less by the school education and have more difficulties in adopting to the current rules of society.

Material

The present investigation comprises a group of ch.o.w. in Copenhagen born on special dates in 1947, whose placing as regards the family milieu has been ascertained on 1/7 1953, i.e. at the age of about 5 years.

Of these 394 ch.o.w. 27 or 7% had died before 1/7 1953. This shows a higher mortality rate than the average, which is 4.5% for the same age.

The family milieu at the age of 5 years for the remaining 367 children is shown in Table 1.

TABLE 1

The family milieu at the age of 5 years for children born out of wedlock in Copenhagen 1947.

	Number	%
With the mother married to the father of the child	118	32.1
With the mother possibly married to the father of the child	85	23.2
With adoptive parents	63	17.2
With the mother, single	54	14.7
With the mother, living with her parents	7	1.9
With the father	2	0.5
With the grandparents	7	1.9
With foster-parents	19	5.2
At infants' homes or other institutions	5	1.4
The child gone abroad with or without the mother	7	1.9
Total	367	100.0

For 32% of the children in question, it has been ascertained that at the age of 5 years they lived in normal families with their own father and mother. Added to this, 23% lived with their married mother, but it has not been possible to state for certain whether the mother was married to the father of the child or to another man. The third largest group was with adoptive parents (17.2%).

Surprisingly, ⅓ of the mothers do not marry before the delivery, even when they later do marry the father of the child. As a motive for this economic advantages such as free delivery and reduced taxes may be mentioned.

At the age of 5 years a total of 82.5% of ch.o.w. are in a normal family milieu with a mother and a father. It may be added that an investigation of the corresponding facts regarding 119 ch.i.w. showed that 90% lived with their father and mother, 5% with the single mother (widow or divorced) and 1% with the mother and a stepfather, 1% lived with the father and 2% had been given away for adoption.

Table 2 shows the age distribution of the unmarried mothers compared with the family milieu of the child at the age of 5 years. All mothers are

young, 28% being under 19 years compared with 15% of all newly married women under 45 years. The more mature mothers more often keep the child as single mothers (¼ are more than 35 years). The younger the mother the more often she gives the child away for adoption.

TABLE 2

The age of the mother years	Own mother and father %	Own mother and father or stepfather %	Own mother %	Adoptive mother and father %	Average %
<19	29	32	11	34	28
20–24	33	38	25	40	34
25–34	30	23	38	23	28
>35	8	7	26	3	10
Total number	118	85	61	96	367

Summary

The present investigation regarding the family milieu at the age of 5 years of children born out of wedlock has shown that 82.5 % live in a home with a father and a mother, either with their own father and mother, a stepfather and their own mother, or with adoptive parents. Corresponding conditions apply to 90 % of children born in wedlock.

The mothers who keep their children as single mothers are considerably older than all other mothers, both unmarried and married.

Les enfants illégitimes à Copenhague. Leur milieu familial à l'âge de 5 ans.

Ce travail porte sur l'étude du milieu familial des enfants illégitimes lorsqu'ils ont atteint l'âge de 5 ans. Il indique que 82,5 % d'entr'eux vivent dans une maison avec leur père et mère — qu'il s'agisse de leur propre père et mère, d'un beau-père et de leur propre mère ou de parents adoptifs. Par comparaison à un groupe homologue, ce pourcentage correspond à une situation identique chez 90 % des enfants nés dans les liens du mariage. Les mères qui gardent leurs enfants avec elles, comme des filles-mères, sont notablement plus agées que les autres, mariées ou non.

Ausserehelich geborene Kinder in Kopenhagen. Ihr Familienmilieu im Alter von fünf Jahren.

Die vorliegende Untersuchung der ausserehelich geborenen Kinder hinsichtlich ihres Familienmilieus im Alter von 5 Jahren hat gezeigt, dass 82,5 % in einem Heim mit Vater und Mutter leben — entweder mit ihrem eigenen Vater und ihrer eigenen Mutter, Stiefvater und eigener Mutter oder mit Adoptiveltern. Unter gleichen Verhältnissen leben 90 % der ehelich geborenen Kinder. Die Mütter, die ihre Kinder allein aufziehen, sind beträchtlich älter als alle übrigen Mütter — das gilt sowohl für die unverheirateten wie für die verheirateten.

Estudio llevado a cabo en la ciudad de Copenague sobre niños nacidos fuera del matrimonio. Su medio familiar al llegar a la edad de 5 años.

La presente investigación fué llevada a cabo para est estudiar el medio familiar de niños nacidos fuera del matrimonio al llegar estos a la edad de 5 años. El 82,5 % viven en un hogar con padre y madre, ya sea con los propios, con padre adoptivo y madre propia o con ambos padres adoptivos. Dicha cifra se eleva al 90 % cuando se trata de niños producto de matrimonios legales. Las madres que solas conservaron sus hijos, fueron considerablemente mayores que las del otro grupo, tanto solteras como casadas.

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Interstitial Pneumonias of the Newborn

by P. W. BRÆSTRUP

During the past 5 years, 17 infants have been treated for pneumonias of atypical forms; the major symptoms and findings are recorded in Table 1. Tachypnoea, cyanosis and pneumonic infiltrations on the X-ray were the most prominent signs.

In accordance with the publications of Golden and Adams, 9 of these cases are classified as atypical chronic pneumonias or virus pneumonias, whereas the last 8 cases, all occurring in 1955—with 2 autopsies (Cases 16 and 17) showing the typical pathology of plasma-cell pneumonia, including the demonstration of *Pneumocystis carinii*—had to be considered as plasma-cell pneumonias. Six of these infants came from 4 different institutions, 2 were cared for in their own homes.

In reviewing these 17 records, it was found that the symptoms (and pathology at the autopsies) had been essentially uniform. This raised the question as to whether it is justified and practical to maintain the classification into special types of the "atypical" pneumonias occurring in early infancy.

If these are roughly outlined as conditions occurring in the first 6 months of life, with the main signs of accelerated respiration, cyanosis, pulmonary infiltrations (often large) on the X-ray, no response to routine antibiotic treatment and negative or non-suggestive bacterial studies, we have to deal with the following commonly described types: (1) Primary atypical pneumonia; (2) viral pneumonia of infants (now commonly identified); (3) plasma-cell pneumonia; (4) giant-cell pneumonia.

A further number of headings, such as: acute bronchiolitis, virus pneumonia, congenital interstitial pneumonias, "Frühgeburt" pneumonias (pneumonias of prematures), interstitial pneumonitis, pseudo-syphilitic chronic pneumonia and others, are now usually accepted either as synonyms for the main groups or possible sub-groups of one of the commonly described types.

The clinical symptoms and course of the 17 cases reported vary sufficiently to overlap all the descriptions given in some 40 publications on the various

TABLE 1

Findings in 17 cases of interstitial pneumonias.

Respiration was above 60 in all cases, several times above 100. *Pulse rate* around 140 for several weeks. Individual figures of 170 to over 200 in several cases. *Temperature:* in 7 infants normal. Only in 4 cases above 38°. *Cold agglutinin titer & ornithosis-reaction:* performed in 6 and 2 cases respectively, were normal. *Bacterial studies:* negative in most cases. In 4 cases staphylococcus albus. *Treatment:* routine sulfathiazole and penicillin to all. O_2 to most and aureo-terramycin to 4 infants. One had erythromycin. Three cases were treated with mepacrine and plasmoquine with little or no effect.

Case no.	Birth weight g	Age (weeks)	Institutional care	Leucocytes	Poly nucl. %	Sedimentation rate mm	Complications	Course (days in hospital)
1	2,200	15	–			40	diarrhoea	relapse of symptoms (110)
2	3,500	9	–			27		mild case (8)
3	3,600	10	+	8,600	43	37	otitis	resp. > 100 for 4 days (17)
4	3,250	4	–			18–32	diarrhoea	medium (32)
5	3,600	9	+	5.000	29	2–6		severe (25)
6	3,100	7	–	16,400	50	26–35		medium (35)
7	3,750	11	+	14,400	19	21		severe (resp. 120) (22)
8	2,950	11	+	21,800	43	25		medium (19)
9	2,300	8	–			11–25	cong. heart dis. (sept. def.)	mild (dead 7 weeks later) (35)
10	3,050	8	+	9,900	37	30		mild (21)
11	3,900	3	–			4–23		severe (dyspnoea 5 weeks) (48)
12	4,100	8	+	8,800	40	34		medium (dyspnoea 5 weeks) (43)
13	2,550	12	+	16,400	37	41	otitis, diarrhoea	severe (50)
14	3,200	5	+			4	diarrhoea	died after 6 days
15	2,900	12	+					died after 3 weeks
16	2,500	12	+	8,800	67	30		died after 4 days
17	3,400	10	+			18	interstitial and mediastinal emphysema	died after 1½ days

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forms of interstitial pneumonia. These descriptions per se overlap eac other in practically all important symptoms. Only the onset may be different: it is usually described as gradual and slow in the reports on "viral" forms, whereas the typical commencement of the plasma-cell cases is diarrhoe or other nonsuggestive symptoms, until the dyspnoea and cyanosis suddenl develop and the infant immediately presents the appearance of being severel ill; usually the child is either premature or in a poor condition for othe reasons. This last description fits most of the 17 cases presented here, i is to be noted, however, that all cases but one of those cared for by skille observers are reported to have had a gradual onset of dyspnoea over some days.

In the 16 cases in which an X-ray was taken, definite, often extensive density was found, and this is noted in all reports dealing with X-ray findings. Two types of X-ray picture are common: either evidence of infiltrations extending from the hilar region and branching out towards the chest wall, or diffuse nodular areas of considerable density. As a rule, the X-ray findings are out of proportion ot the scanty physical changes, and are often also associated with a relatively unimpaired general condition of the child.

Descriptions of X-ray films, and in particular the films reproduced in various publications, are essentially identical. For example, the films reproduced by Adams and Sternberg & Rosenthal, respectively, are suggestive, although both are described as typical of two differently named and characterized conditions.

As to the etiology, some confusion has been caused by the description of the *Pneumocystis carinii*, a protozoon found and named by Vanek and Jirovec, and suggested as the etiologic factor of the plasma-cell pneumonia. This conception is largely accepted in several publications from Czechoslovakia and Germany. It is evident that this protozoon is now found in almost every case of plasma-cell pneumonia when thoroughly looked for, and is often easily recognised in published photomicrographs where the author himself has not described it. As stated by Carlberg and Nathorst-Windahl, this is the case in Fig. 2 of Gormsen's publication, and is certainly also the case in Fig. 3 of Wolmann and co-workers' Case 1, reported as a giant-cell pneumonia. It can only be a question of a short time until it is first demonstrated on the other side of the Atlantic.

The significance of *Pneumocystis carinii* is also claimed on the basis of favourable therapeutic results with anti-plasmodic therapeutics such as atebrine, mepacrine and plasmoquine. Later however, these drugs have been tried with negative results, as also in three of the cases presented here. The *Pneumocystis carinii* is also found in children who have died from other diseases (Fingerland & Vortel), and its etiological significance needs further support to be generally accepted.

The pathologic description of all the different conditions dealt with here is essentially that of heavy, red, wet lungs with very little air, except for the marginal regions, which are often emphysematous; obstructive and interstitial emphysema as seen in Case 17 seems to be a relatively frequent finding. At microscopy, the bronchioles do not contain cells in the lumen, and their walls and surroundings are relatively free from pathologic changes, this being in particular contrast to classical bacterial pneumonia. In the interstitial tissue around the alveoli, and in the interalveolar septa, huge amounts of mono-nuclear cells, mainly plasma cells, monocytes and macrophages are found, and this picture, with very slight variations, is identical in all the different forms of interstitial pneumonias described.

Lars Ström, dealing apparently mainly with patients over one year of age, suggests the term *interstitial pneumonia*—as first introduced by Lenk—to cover some 13 different names and types. Evidently, this general term could also be given to all atypical pneumonias of the newborn infant, hitherto specified as a number of different types.

Summary

Seventeen cases of interstitial penumonia in children under 15 weeks af age are reported. Only 2 patients were premature. Four died. In the case of the 2 who died after 1951, *Pneumocystis carinii* was demonstrated.

It is stated that these 17 cases, in their symptoms, clinical findings and pathology, cover all the characteristics of a number of different forms of viral, atypical and plasma-cell pneumonias, and it is suggested that sufficient data are not available to support the specification of various forms. All these pneumonias should be dealt with as a clinical entity named *interstitial pneumonia of the newborn.*

La pneumonie interstitielle du nouveau-né.

Dix sept cas de pneumonie interstitielle chez des enfants de moins de quinze semaines ont été étudiés. Deux d'entr'eux seulement étaient des prématurés. Quatre moururent. Parmi les deux dont le décès survint après 1951, la présence de *Pneumocystis carinii* fut notée. L'auteur indique que ses 17 cas, par leurs symptômes, leurs aspects clinique et anatomo-pathologique, traduisent l'existence de formes diverses de pneumonies, qu'il s'agisse de pneumonies virales, atypiques ou plasmocellulaires. Il lui semble qu'il n'existe pas suffisamment de données permettant de classer de façon précise ces différentes formes. Aussi peut-on réunir toutes ces pneumonies sous le nom de l'entité clinique suivante : *Pneumonie interstitielle du nouveau-né.*

Interstitielle Pneumonie der Neugeborenen.

Es wird über siebzehn Fälle von interstitieller Pneumonie bei Kindern unter 15 Wochen berichtet. Nur 2 von ihnen waren Frühgeborene. 4 Kinder starben. Bei den 2 Kindern, die nach 1951 starben, wurden *Pneumocystis carinii* nachgewiesen. Es wird dargestellt, dass diese 17 Fälle in ihren Symptomen, ihren klinischen Erscheinungen und ihrer Pathologie die Charakteristika verschiedener Pneumonieformen — der

Viruspneumonie, der atypischen Pneumonie und der plasmacellulären Pneumonie – aufwiesen, und es wird angedeutet, dass eine Unterscheidung der verschiedenen Formen klinisch nicht möglich ist. Alle diese Pneumonien sollten in einem klinischen Gesamtbegriff mit dem Namen *interstitielle Pneumonie der Neugeborenen* zusammengefasst werden.

Neumonías intersticiales en el recién nacido.

Se comunican 17 casos de neumonía intersticial en lactantes menores de 15 semanas de edad, solo 2 de ellos prematuros. Cuatro casos fueron fatales, los dos que murieron antes de 1951 evidenciaron la presencia de *Pneumocystis carinii*. Los síntomas, hallazgos clínicos y patológicos de estos 17 casos cubren todas las características de las diferentes formas de neumonías atípicas, virales y plasmacelulares. Los datos no son suficientes para afirmar la especificidad de las diferentes formas. Todas estas neumonias deben ser encuadradas en la entidad clínica conocida como *neumonia intersticial del recién nacido.*

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From the Queen Louise Hospital for Children, Copenhagen
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Non-specific Spondylitis in Childhood

by ANNALISE DUPONT and HENNING ANDERSEN

Non-specific osteomyelitis affects the vertebral column in 1–2% (Kærn, Balthazar). Out of Kærn's 340 cases 36 were children aged 1–10 years. Non-specific spondylitis exclusively in children has been reported by Wissler, Saenger, Bremner & Nelligan, and children are also included in series published by Butler & Blusger, Martin, Agerholm & Trueta, Guri, Tucker & Hollenberg, and Hellner.

Aetiology.—The most common exciting organisms are staphylococci or pathogenic intestinal bacteria (Hellner). Recent publications (Balthazar) indicate the aetiological significance of traumata.

As a rule, the lesion is localized to the lumbar or the lower dorsal vertebrae, usually affecting the bodies.

Symptoms.—In the acute, often fulminant variety, the clinical signs are dominated by focal symptoms and/or generalized infection (sepsis). The subacute, often insidious variety commences with an afebrile or subfebrile stage with fatigue and anorexia, followed, in a few weeks, by increasing local symptoms. In this stage Guri makes a distinction between four types: the *hip-joint, abdominal, meningeal,* and *backpain* syndrome—according to which symptoms predominate.

Diagnosis.—If the condition is dominated by generalized infection, it may be difficult to diagnose in the initial stage. As regards the subacute variety, the differential diagnostic possibilities may be seen from the above-mentioned 4 clinical types. Radiological changes—narrowing of an intervertebral space and erosion of the adjacent bony surfaces—do not appear until some time has passed. Progressive destruction may give rise to kyphosis, scoliosis, posterior dislocation fusion of the vertebrae, etc. Regeneration occurs within the first few months. This fact as well as the absence of halisteresis are important in differentiating the condition from tuberculosis. Tomography may afford valuable information about the extent of the lesion (Cases 3 and 4).

In view of the almost invariable involvement of the disc, the disease has been named spondylarthritis by some authors, e.g. Saenger.

Prognosis and Treatment.—In Kærn's series 11 out of the 36 children between 1 and 10 years of age died. A benign course has been reported by Wissler, Saenger as well as Bremner & Nelligan—in a total of 15 cases. This cannot be due exclusively to modern antibacterial therapy, as in Bremner & Nelligan's series of 7 children aged 9 months to 2½ years all recovered after 4–6 weeks' treatment in a plaster cast, not supplemented by antibiotics except in 1 case (penicillin). While all authors seem to be agreed that immobilization is essential at least for the duration of the destructive phase, the indications for antibacterial therapy are not definitely established.

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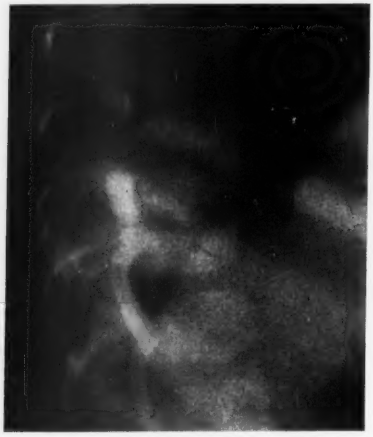

Fig. 1. Case 1 in the acute stage. Narrowing of the intervertebral disc between D 10 and 11; destruction and collapse of the two adjacent vertebral bodies.

Authors' Cases

During the past 4 years 4 patients with non-specific spondylitis have been admitted to the Queen Louise Hospital for Children.

Case 1. S. P., case rec. 45/52. A girl, aged 21 months, who had so far been in good health, suddenly developed high fever, meningism, and faucial reddening. Spinal fluid normal. After a few days' penicillin therapy the patient had apparently recovered.

When, 10 days later, the temperature increased again, she was admitted to the Queen Louise Hospital for Children. On admission she exhibited gibbus at the site of D 10. X-ray findings: Narrowing of the disc between D 10 and 11, erosion of the adjacent bodies, no halisteresis, no paravertebral abscess, lungs normal. Repeated tuberculin tests negative. Widal negative, E.S.R. 70 mm/hour, W.B.C. 15,800 with 50 % polynuclears. Blood cultures revealed *Staph. albus.*

Treated with penicillin + sulphathiazole for one week, kept in plaster cast for one month, and then in a splint at night for 8 months. The patient was quickly rendered symptom-free and was discharged at the end of 6 weeks with a normal E.S.R. and W.B.C.; the bony lesion was regenerating.

At follow-up, 4 years later, good mobility of the back. X-ray showed fusion of D 10 and 11.

Case 2. J. S., case rec. 1464/55. A boy, aged 3½ years, who had previously been in good health, sustained an injury to the mid-back, resulting in a local haematoma and tenderness persisting for one week. No symptoms during the next month. Thereupon, the patient began to complain of "stomach ache" and increasing stiffness of the loin, so he was admitted to the Queen Louise Hospital for Children. On admission physical examination showed a gibbus at the site of the fixed area, but no other abnormality. X-rays revealed a collapsed disc between L 1 and 2, destruction of the contiguous bony surfaces, no halisteresis, no paravertebral abscess.

Fig. 2. Case 3. X-ray film showing the changes in the lower part of the dorsal column as well as the paravertebral abscess.

Mantoux: + (BCG vaccination one year previously). Widal negative. E.S.R. 45 mm/hour, W.B.C. 15,600 with 65 % polynuclears.

Kept in a plaster cast for 3 months and thereupon in a splint at night for 6 months. No antibacterial therapy was given. E.S.R. and W.B.C. normalized within one month. In a few months the bony lesion was regenerating, and the patient was discharged.

At follow-up 3½ years later he was feeling well. There was a mild, S-shaped scoliosis and a trace of gibbus, but normal mobility. X-rays showed narrowing of the intervertebral space and slight sclerosis of the adjacent bony surfaces.

Case 3. A. E. O., case rec. 312/54. Girl, aged 8 years 9 months, previously in good health. She developed fever with back pain suddenly and later abdominal pain. She was subjected to appendectomy which showed an appendix with slight gross and microscopic changes. In connection with the operation the patient had high fever and marked stiffness of the back. Spinal fluid normal. Treated with penicillin for one week and discharged feeling well.

Two weeks later the patient was admitted to the Queen Louise Hospital for Children because of fluctuating temperature, fatigue, and an elevated sedimentation rate. On admission she was running a low-grade fever. She had a gibbus at the site of D 10 and was holding this part of the back very rigid. Strikingly brisk deep reflexes in the

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Fig. 3. Tomogram in Case 3 showing destruction and posterior displacement of D 11 as well as narrowing of the intervertebral space and destruction of D 12.

lower limbs. X-rays revealed destruction anteriorly in the body of D 10, narrowing of the underlying intervertebral space, and a paravertebral abscess. No halistere-sis. Mantoux: + (BCG vaccination 3 years previously). Chest radiography: Normal. Widal negative. Staphylococcus antitoxin titre constantly elevated through several months. E.S.R. and W.B.C. elevated.

Treatment: Penicillin, 200,000–600,000 units daily for 4 weeks, plaster cast for 2 months. The paravertebral abscess and temperature yielded, and the E.S.R. and W.B.C. were normalized. Tomography showed that the posterior margin of D 11 projected into the spinal canal (Fig. 3). For this reason, and in order to speed the healing of the bone lesion, a Hallstead *spondylodesis* was performed in the Orthopaedic Hospital. The postoperative course was uneventful, and the patient was discharged for out-patient treatment with braces of different kinds. Ever since, she has been feeling well. In particular there have not been any signs from the central nervous system.

Follow-up 2½ years later showed no abnormality apart from slight collapse and sclerosis of the affected vertebrae.

Case 4. J. F., case rec. 1027/55. Boy, aged 7. Insidious onset with low-grade fever, headache, limping, and pain in the left flank. X-rays of the spine failed to show any abnormality. After a 3-week symptom free interval, he had a recurrence of the above-mentioned symptoms and was admitted to the Queen Louise Hospital for Children. Admission findings: Fixation of the lower part of the back, gait marked by a throwing forward of the left hip. Increasing pain in the back and flank owing to muscular fixation, simulating pareses of the lumbosacral, abdominal, iliopsoas, and median gluteal muscles. X-rays of the spine, including tomography, showed narrowing

of the intervertebral space L 4–5 and erosion of the contiguous vertebrae. No paravertebral abscess or halisteresis.

Cerebrospinal fluid: No abnormality. Widal negative, tuberculin skin test negative, E.S.R. 28 mm/hour, rapidly decreasing, W.B.C. 9800.

Treatment: Penicillin, 1 million units daily for 36 days, achromycin for 6 days, plastic cast for 6 weeks, thereupon a splint at night. Course: Twelve days after admission pus was voided per rectum (culture negative for pathogenic intestinal bacteria or staphylococci). This was immediately followed by improvement of the general condition as well as the local symptoms.

Follow-up: 2 months. No kyphosis or scoliosis, good mobility of the spine. X-rays: Osteosclerosis of the involved vertebral bodies and narrowing of the intervertebral space.

Discussion

Our 4 patients represent all 4 syndromes set up by Guri. Case 1 had *meningeal* symptoms. Although it cannot be entirely ruled out that the disease commenced as pharyngitis with meningism and was later complicated by spondylitis, it is more likely that the entire course is explicable as spondylitis with an initial stage of meningeal symptoms. The symptoms in Case 2 correspond to Guri's *back-pain syndrome*. Case 3 can naturally be classified as the *abdominal syndrome*. However, in this case also it is impossible to tell with certainty whether the spondylitis was primary or whether it is interpretable as a complication of appendicitis. In Case 4 the symptoms correspond exactly to the *hip-joint syndrome*, there being a mixture of muscular spasms and pseudopareses in conjunction with low-grade fever which gave rise to a suspicion of poliomyelitis. Most probably staphylococcal infections were responsible in Cases 1 and 3. In Case 4 the aetiology is not clear. It is difficult to decide whether the evacuated pus was related to the skeletal lesion. Trauma may have been the cause of the disease in Case 2. According to Balthazar, the trauma must have been a severe one and it must have occurred a minimum of 19 days and a maximum of 8 weeks prior to onset. Both conditions are fulfilled in Case 2.

Summary

The authors report 4 cases of non-specific spondylitis in children aged 1–10 years. These 4 patients presented 4 widely different syndromes: Meningeal, back-pain, abdominal, and hip-joint syndromes. The aetiology seems to have been staphylococcal infection in 2 cases.

Spondylite non spécifique dans l'enfance.

L'auteur rapport 4 cas de spondylite non spécifique chez des enfants âgés de 1 à 10 ans. Ces quatre malades présentaient 4 syndromes absolument différents : tableau de méningite, de douleur dorsale, de coxarthrie et syndrome abdominal. Dans deux cas, l'étiologie semblait imputable à une infection staphylococcique.

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Unspezifische Spondylitis im Kindesalter.

Die Autorin berichtet über 4 Fälle von unspezifischer Spondylitis bei Kindern im Alter von 1–10 Jahren. Diese 4 Patienten wiesen 4 verschiedene Syndrome auf: Meningiale Erscheinungen, Rückenschmerzen, abdominelle Beschwerden und Hüftgelenkssymptome. Ätiologisch kommt in 2 Fällen eine Staphylokokken-Infektion in Frage.

Espondilitis inespecífica en la infancia.

El autor comunica 4 casos de espondilitis no específica en niños entre 1 y 10 años de edad. Presentaron 4 síndromes diferentes: Meningeo, dolor dorsal, abdominal y de la articulación de la cadera. En 2 casos, la etiología pareció ser estafilocócica.

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Prolonged Icterus Neonatorum and Congenital Myxedema

by J. FLAMAND CHRISTENSEN

In 1954, Åkerrén called attention to the fact that prolonged physiologic jaundice of the newborn (icterus neonatorum prolongatus) may occur in infants with congenital myxedema. He discussed three cases of his own observation and seven more which were seen by others. Since the two diseases are rare, he supposed that the simultaneous appearance could not be due to chance but must be based on an interrelationship or a common cause, an assumption which will increase in probability the more frequently this combination is observed.

In the last 8 years, 11 infants with congenital myxedema were treated in the children's department in Odense. Five of them had icterus of more than two months' duration after birth. One of the infants was admitted at the age of two months because of the persistent jaundice; only the history of this patient will be reported in detail. The others were admitted after the icterus had disappeared. The most important data of the five children are given in Table 1.

Case Report (Case 5).—Boy, normal delivery on 18 May 1954. Birth weight 2900 g. He became icteric at 2–3 days of age. No cerebral symptoms at any time, good condition at the beginning. Admitted 6 August 1954 because of persistent icterus. He was short, plump and limp, with thick eyelids, large tongue, rough voice, and the skin was deeply jaundiced and leather-like. Marked constant nystagmus.

Skin biopsy showed myxedematous changes. Hb.: 74 %, erythrocytes: 3.16 mill., leucocytes: 5240 with a normal blood picture. Coombs' test negative. Blood type: A Rh pos. (mother: O Rh pos.). Serum cholesterol on 7/8: 234 mg %, on 13/9: 144 mg %. Serum bilirubin on 7/8: 21.2 mg %, on 19/8: 4.4 mg %, on 13/9: 1.0 mg %. Feces were always of normal colour, and the urine was light coloured and gave a negative reaction for bilirubin and urobilin.

With thyroid therapy the general condition improved rapidly; the jaundice disappeared in the course of a few weeks. At later examinations, the somatic growth has been good but there is still a nystagmus, a defect of vision and presumably a hearing defect, and definite mental retardation.

TABLE 1

Sex	Age on admission	Birth weight g	Duration of icterus months	Age at diagnosis of myxedema months	Mental devt.	Blood type
F	11 yrs	4700	6–8	10	I.Q. 63	Mother: O Rh pos.
F	9 yrs	4800	3–4	5	normal	Father: O Rh neg.
F	10 yrs	over 3500	3	8	I.Q. 67	A Rh pos. Mother: A Rh pos.
M	5 mths	4550	3	5	imbecile	A Rh neg. Mother: A Rh neg.
M	2 mths	2900	3	2	imbecile?	A Rh pos. Mother: O Rh pos.

All 5 cases had typical myxedema symptoms during the first months after birth, and jaundice from 2–3 days of age for at least 3 months. The icterus had, in all cases, the appearance of a prolonged physiologic icterus. The bowel movements were of normal color, and there was no marked anemia. Isoimmunisation on the basis of blood group incompatibility is excluded in all cases—or very unlikely. Definite mental retardation was found in 4 children, and eye symptoms in the form of severe strabismus or nystagmus, likewise in 4.

Discussion

These five cases correspond closely to the ones reported by Åkerrén. It is therefore probable that this combined syndrome is relatively common—as has also been asserted by Vahlquist—and does not depend on coincidence but on a mutual relationship of the two entities.

It is unlikely that the jaundice can be the cause of the hypothyroid state, one of the reasons being that such a combination is never seen with icterus due to erythroblastosis or primary liver or biliary tract diseases. It is likewise improbable that the congenital thyroid defect is the only, or the most important, cause of the infant's jaundice. Presumably it is a matter of physiologic icterus neonatorum which persists for an especially long time due to the hypothyroidism.

The most important causes of neonatal icterus are the postnatal hemolysis

and hepatic immaturity. Signs of increased or prolonged hemolysis have not been demonstrated in any of the reported cases. On the other hand it is probable that the neonatal immaturity of different organs will continue for a longer period in athyroid infants and in this way extend the duration of jaundice. "The degree of hyperbilirubinemia is a measure of the functional maturity of the infant at the time of birth" (Davidson, Merritt & Weech). It is reasonable to believe that beside immaturity of the liver, an immature renal function is also of significance for the degree and duration of icterus. In all the cases where information about the urine is available (Åkerrén's Cases 1, 2, 3, 4, 5, 7 and our Case 5), the urine was found to be normal; it did not contain bilirubin. The threshold for the appearance of bilirubinuria is variable and especially high in hemolytic icterus and icterus neonatorum (With), so that bilirubinuria is rarely encountered in the latter condition. Yet it may appear strange that cases with an icterus with serum bilirubin levels of 12.5 mg% (Åkerrén's Case 1) and 21,2 mg% (our Case 5) do not show excretion of bilirubin in the urine. The very low bilirubin clearance, on this occasion, like the low urea and inulin clearance in young infants, may be due to an incomplete development of renal function, and this defective state probably continues longer when the infant has myxedema.

The visible icterus depends mainly on a deposition of bilirubin in the tissues and only to a less degree on the colour of the tissue fluids and serum. In physiologic jaundice there is, however, no fixed relationship between the degree of visible jaundice and bilirubinemia. "Obviously some skins must reveal icterus more easily than do others" (Smith). It is possible that the characteristic myxedematous skin changes bring along an increased affinity for bilirubin.

In this connection it would be interesting if it could be shown that the icterus disappeared faster with thyroid therapy than without such treatment. In the cases in which treatment was begun while the infant was icteric, the jaundice decreased rapidly concurrently with the myxedematous signs. In the other cases, however, it disappeared spontaneously in spite of persisting signs of myxedema. The treatment appears to have speeded up the disappearance of the icterus but a definite comparison between treated and untreated cases is not possible.

The question naturally arises whether the combination of icterus with myxedema points to an especially grave prognosis, particularly in regard to cerebral damage, as is the case in kernicterus in connection with erythroblastosis, prematurity or other severe debility.

Thus normal mental development was found in only one of my 5 cases, and in one of Åkerrén's 3; in the others, signs of cerebral damage with marked intellectual defects and severe strabismus and nystagmus were present.

In ordinary physiologic icterus in non debilitated infants, or in jaundice due to liver or biliary tract disturbances, cerebral damage is, however, never seen. It might be assumed, nevertheless, that the brain cells in myxedema have been primarily affected to such an extent that they are especially sensitive to a toxic effect of bilirubin or its derivatives. This would correspond to the probable pathogenesis of kernicterus.

In the cases here described acute neurological symptoms such as are typical for kernicterus were, however, never seen, and even though permanent cerebral damage as a consequence of kernicterus may become manifest only as a mental or sensorial defect, the typical picture in such cases is based on the damage of the basal nuclei with athetosis and dystonia— a symptom complex which is not seen in connection with myxedema.

Besides, equally severe cerebral defects as in the described cases, are not seldom found in congenital myxedema without jaundice. It is therefore hardly justified to make the bilirubinemia responsible for the poor prognosis.

It is peculiar that the birth weights of 4 of these infants were strikingly high: 4700 g, 4800 g. "more than 3500 g", and 4550 g; only in Case 5 was it rather low, 2900 g. In Åkerrén's first and third cases, the birth weights were 4160 g and about 4000 g, respectively, in his second report it is not mentioned, and among the cases quoted by him, Wallgren's weighed 3200 g and Vahlquist's 4300 g, while the weights are not given in the rest.

Most of these infants are thus large at birth. This is noteworthy considering that prolonged neonatal jaundice is much more frequent among infants with a low than among those with a high birth weight. Beskow encountered icterus of more than 14 days' duration in 48.7% of infants weighing less than 2500 g at birth, but in only 5.7% of those weighing more than 3500 g. However, of the 6 infants with congenital myxedema without icterus who were treated during the same period on the ward, 4 also had high birth weights (4900 g, 4300 g, 4200 g, 4100 g). It is possible that this fact is characteristic for infants with congenital myxedema, but I have not seen it described earlier. If this is the case, it may be due to the influence of an abnormal hormone balance which affects these infants already before birth.

The prognosis in myxedema giving symptoms during the first months of life is always doubtful and most often poor, and irreparable damage may possibly be present already at birth. Still it may be considered to be of the greatest importance to start therapy as early as possible.

The recognition that a prolonged icterus in a newborn may be the first sign of congenital myxedema can help significantly in arriving at an early diagnosis.

Summary

Among 11 cases of congenital myxedema, five had prolonged neonatal icterus of more than two months duration. It is assumed that the slow maturation of the organs in congenital myxedema results in a deepening and prolongation of a physiologic icterus.

A prolonged physiologic icterus may consequently be the first sign of myxedema and in this way help in arriving at an early diagnosis.

The 11 infants with congenital myxedema had an average birth weight of 3950 g, and 7 weighed between 4100 g and 4900 g. High birth weight was found among jaundiced as well as non-icteric infants. It is assumed that a high birth weight with congenital myxedema can be due to a prenatal disturbance of the hormonal balance.

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From the Municipal Out-Patient Clinic for Allergic Diseases in Children, Copenhagen
(Head: E. WINGE FLENSBORG)

Sex Variations of Cutaneous Reactions in Asthmatic Children

by E. WINGE FLENSBORG

It is generally known that asthma occurs twice as often in boys as in girls (3, 4, 5, 12), but in acute asthmatic bronchitis in infancy and early childhood the same sex difference is also found (1, 8). In reports concerning sex differences in infantile eczema and Besnier's prurigo, the results are somewhat different (2, 4, 10) and suggest a higher incidence in girls. In allergic diseases in childhood altogether, a higher incidence among boys has been demonstrated in children aged 0–10 years; conversely, the incidence at puberty is higher in girls (4, 9). The differences between allergic boys and girls, however, are more profound. Asthma starts earlier in boys than in girls (3, 4, 5), and in the tendency to spontaneous cure there seems to be a difference too: the asthmatic attacks cease, on the average, somewhat earlier in girls (5). Furthermore, a sex difference exists concerning frequency and strength of positive skin tests: boys, on the average, react more often and more strongly positively than girls (3, 6).

A more acurate analysis of the sex differences in skin reactions in different age groups and with different allergens does not seem to have been published earlier.

Own Investigations

Scratch tests with a considerable number of allergens (inhalants and foodstuffs) were carried out in 853 children with the diagnosis of bronchial asthma and/or asthmatic bronchitis. Five hundred and seventy-three (67

TABLE 1

Results of scratch tests in 853 asthmatic children.

Groups of allergens	Boys		Girls	
	Number of scratch tests	Per cent positive	Number of scratch tests	Per cent positive
Animal hairs	4,798	4.6	2,282	4.4
Feathers	725	31.9	349	28.9
Dust of feathers	568	31.7	282	21.3
House-dust (purified)	653	44.9	330	31.5
Pollen	676	10.3	304	8.2
Moulds	585	4.0	278	4.7
Textiles	1,419	1,9	691	1.6
Foodstuffs	2,700	3.4	1,379	1.7
Total	12,124	9.5	5,895	7.3

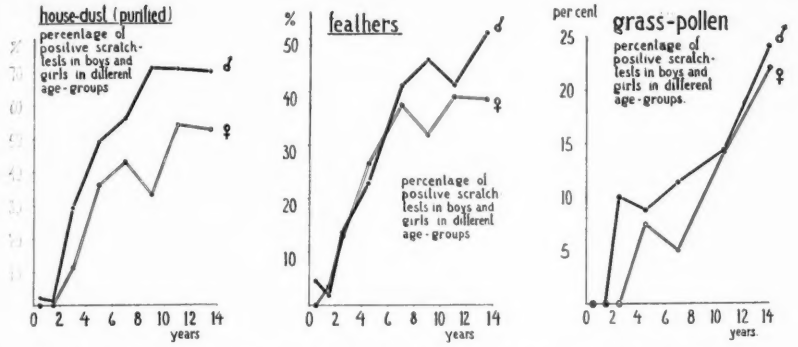
house-dust (purified)
percentage of positive scratch-tests in boys and girls in different age-groups
feathers
percentage of positive scratch tests in boys and girls in different age-groups
grass-pollen
percentage of positive scratch-tests in boys and girls in different age-groups.
per cent
%
years

Fig. 1. Incidence of positive scratch tests with inhalants in various ages in asthmatic boys and girls.

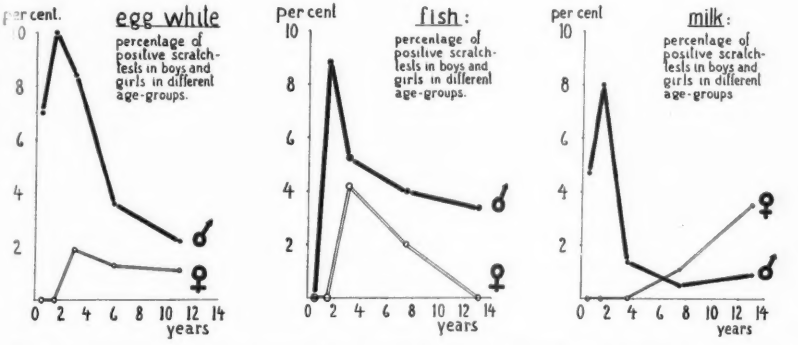
egg white
percentage of positive scratch-tests in boys and girls in different age-groups.
fish:
percentage of positive scratch-tests in boys and girls in different age-groups.
milk:
percentage of positive scratch-tests in boys and girls in different age-groups
per cent.
years

Fig. 2. Incidence of positive scratch tests with foodstuffs in different ages in asthmatic boys and girls.

per cent) were boys, 280 (33 per cent) girls. Many of the children have been tested two to several times at intervals from half a year to three years. A total of 18,000 scratch tests has been done, 12,000 in boys and 5900 in girls, with 9.5 per cent and 7.3 per cent positive reactions, repectively. Only definitely urticarial, sharply and irregularly delimited immediate reactions were registered as positive.

In almost all groups of allergens, the incidence of positive scratch reactions is higher in boys than in girls, but for some of the groups the difference is only minimal. Since the frequency of positive scratch reactions varies much in different age groups (6, 7), more exact information will be obtained by an analysis of the reactions with the individual allergens in different ages (Figs. 1 and 2).

Fig. 1 demonstrates that boys of all ages more frequently than girls react positively to scratch tests with inhalants. This is most marked when house dust is concerned, but the same tendency is obvious in the results with feathers and pollen.

Fig. 2 shows that the incidence of positive scratch tests with foodstuffs, as distinct from inhalants, decreases with increasing age, but with regard to the sex difference the findings are the same: boys react positively more frequently than do girls, and this holds true for all age groups (exception: cow's milk in children more than 6 years of age).

Altogether it has been demonstrated that in all ages with almost all allergens, asthmatic boys react more frequently positively than do asthmatic girls.

A definite cause for the sex differences demonstrated in the present and earlier papers has not been given, but hormonal differences may be the cause.

Summary

In 853 asthmatic children it was found that boys in all age groups and with almost all allergens reacted more often positively to scratch tests than did girls.

Variations dans les épreuves cutanées de sensibilisation chez des enfants asthmatiques en fonction de leur sexe.

L'auteur indique que, chez 853 enfants asthmatiques, les garçons réagissaient mieux que les filles aux scratch-tests, quel que soit leur âge, ou l'allergène en cause.

Geschlechts-Variationen von Cutan-Reaktionen bei asthmatischen Kindern.

Bei der Untersuchung von 853 asthmatischen Kindern ergab sich, dass Knaben in allen Altersgruppen und mit fast allen Allergenen bei Haut-Skarifikationstesten öfter positiv reagierten als Mädchen.

Las reacciones cutàneas en niños asmáticos. Su relación con el sexo.

Se estudiaron 853 niños asmáticos encontrándose que los varones, independientemente de la edad y casi con todos los alergenos, dan mas amenudos que las niñas reacciones cutáneas positivas.

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From Dronning Louises Children's Hospital (Chief: Prof. O. ANDERSEN)

Neonatal Hepatitis with Osteomalacia

by BENT FRIIS-HANSEN

A case of long-standing neonatal hepatitis has recently been admitted. The patient had developed extensive osteomalacia, but recovered subsequently. The case is presented since it illustrates the connection between bone metabolism and liver disease.

The etiology of neonatal hepatitis has been investigated by Stokes. He studied 12 infants in whom the symptoms of hepatitis began during the first 2 months of life, and he came to the conclusion that transplacental infection with homologous serum hepatitis virus was the most reasonable explanation. This theory was supported by the observation that he was able to transmit serum hepatitis virus to human volunteers by injecting blood from both one of the infants and the mother.

On the other hand, it must be mentioned that not all siblings of mothers who have given birth to a child with neonatal hepatitis develop this disease. Gellis and collaborators have reported that at least 35 siblings from 25 such families did not show any signs of neonatal hepatitis, and only in 4 cases siblings younger than the affected child developed this condition. A few other cases of familial hepatitis have been reported (Adams) but these cases may in some instances have been caused by hereditary metabolic disorders.

The theory of transplacental infection is further supported by the observation by Drake that most patients infected by the virus of homologous serum hepatitis often do not develop antibodies, and are thus prone to become silent carriers. This is in contrast to the well known fact that immunity quickly develops after infection with infectious hepatitis. Therefore, infection from mother to child with this disease seems to be rare.

Hsia *et al.* carried out a follow-up study on 11 children whose mothers had suffered from infectious hepatitis during pregnancy. They reported that no case of hepatitis developed in the neonatal period, or later.

As a conclusion of these observations, it may be stated that there is strong evidence that most cases of neonatal hepatitis are caused by transplacental infection with homologous serum hepatitis which is known to have an incubation time of 60–150 days, whereas the incubation time of infectious hepatitis virus is only 10–40 days.

In cases of neonatal hepatitis beginning after the first few months of life, both etiologies must be considered.

The microscopic picture of the diseased liver in infants suffering from neonatal hepatitis is characterized by inflammatory reactions and large, multinucleated giant liver cells. These cells are believed to represent regeneratory processes of the liver of the fetus or the young infant (Craig and Landing). A very similar microscopic picture has been seen in infants that suffered from hemolytic jaundice and erythroblastosis (Anderson) and has been observed in young children (Traisman *et al.*) and even in an adult (Klucké) with chronic hepatitis, and the giant cells alone are therefore not specific for virus hepatitis in the newborn.

Viral hepatitis in infancy is a rare disease but it is often followed by cirrhosis, and the mortality rate is high, about 50% (Stokes and Craig *et al.*). In contrast to this, a follow-up of 200 cases of infectious hepatitis in children did not reveal any case of cirrhosis (Craig).

Case Report

Girl L. N. (537/55) was admitted to the Hospital 13 months old. She is no. 3 of 3. The two siblings are well and have never suffered from jaundice. The mother has suffered from gallbladder stones for 5 years and had icterus during one attack, but denies hepatitis.

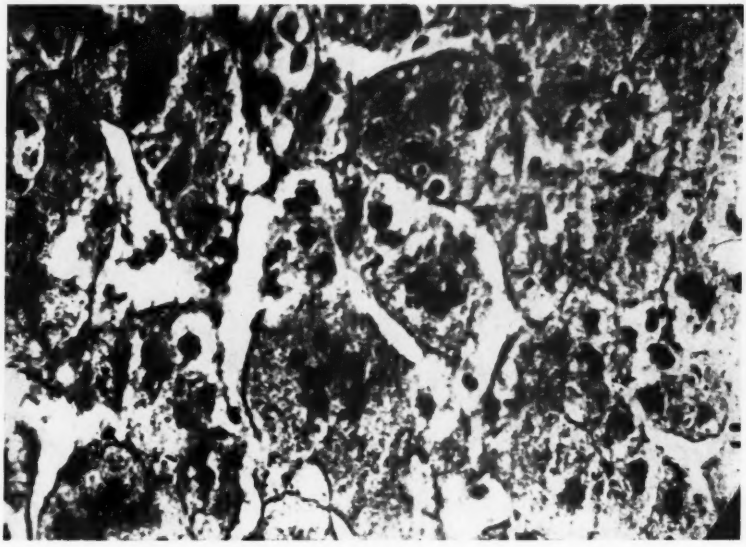

Fig. 1. Liver biopsy with the multinucleated parenchymal cells and no signs of biliary cirrhosis.

Fig. 2. The bones of the lower extremities: before (A) and after 1 month (B) and 5 months (C and D) of treatment.

The patient had slight neonatal jaundice which disappeared completely. At two months of age she developed severe jaundice, and two months later an exploratory laparotomy was performed and, as the external biliary system proved to be normal, a liver biopsy was taken.

The microscopic picture showed degenerative changes and inflammatory reactions, and scattered large multinucleated parenchymal cells (Fig. 1). The child went home, icterus persisted, and at 13 months of age the child was admitted to Dronning Louises Children's Hospital in a very poor condition. She was small, atrophic and with greyish jaundice. She had shallow respiration due to softness of the ribs. The bones were tender and so soft that the extremities could be bend in any direction, as if there had been no bones at all. The urine was dark and the stools light but not bulky or greasy, and no fat was seen on microscopic examination. She was treated with blood transfusions, antibiotics, water-soluble vitamins: A (10,000 units per day), D (2000 units per day), B, C, E and K, and received supplements of calcium chloride and protein hydrolysates in the diet.

The child recovered slowly during the following months, icterus disappeared, the colour of the stools and urine became normal, and X-ray examination showed recalcification of the bones (Fig. 2).

Laboratory examinations on admission showed: icterus index 35 (Meulengracht), serum bilirubin 4.2 mg %, serum calcium 4.1 meq, serum phosphorus 2.6 meq, alkaline phosphatases 142 units (King-Armstrong), pH of the blood 7.46, prothrombin time 28 sec. (norm. 18 sec.), erythrocyte sedimentation rate 19 mm/hr. After two months of treatment these values returned to normal except that the phosphatases remained elevated (40–60 units) and the prothrombin time was unchanged. Other analyses gave essentially normal results; these included serum proteins (fractionated and by electrophoresis), white cell count and platelets, total carbon dioxide, chloride, sodium, potassium, blood urea, thymol extinction and routine urine examination.

On admission the urine contained large amounts of aminoacids: glutamin, alanin and lysin. On several later occasions no abnormal excretion of aminoacids was found.

From the above-mentioned facts, there is strong evidence that this case of neonatal hepatitis has been infected with homologous serum hepatitis virus directly from the mother. The case was complicated by an extensive osteomalacia.

Liver disease may, like celiac disease, lead to rickets due to defective absorption of vitamin D. However, this complication is fairly rare. Craig, Gellis & Hsia who have studied more than a hundred children with liver cirrhosis do not describe any case of bone disease in their material. But when the two diseases are seen at the same time this may be related to a direct connection between liver and bone metabolism. This relationship is indicated by several observations.

It has been shown that much larger quantities of vitamin D were required, even when administered parenterally, to effect cure in rachitic rats, when the liver was injured (Heyman). A similar observation was made in dogs with injured livers (Greenberg) where injection of parathyroid extract failed to increase the level of serum calcium. Gerstenberger reported that certain cases of cirrhosis of the liver may develop rickets in spite of adequate antiracitic measures.

Three cases of fatal liver disease with extensive osteoporosis have been reported (Hansen, Ziegler & McQuaurrie and Roberts & Sullivan). In these

patients jaundice was mild or absent, and in one case recalcification of the bones took place.

In spite of the fact that osteomalacia rarely is seen in patients with liver disease, these observations may support the theory that the osteomalacia is due to lack of some unknown factor normally present that promotes calcification or prevents decalcification ("hepatic rickets" (Gerstenberger)).

The severe osteomalacia seen in this child might of course be explained as a result of acholic stools with defective absorption. However, the mother claimed that she had given the child a proper diet and vitamin D preparations at home, and denies that the patient at any time had periods of diarrhoea or steatorrhoea. Furthermore she had gained 2 kg of weight during the period at which the osteomalacia developed. At admission the decalcification was so severe that it seems reasonable to believe that other factors have been at play. The low serum calcium and low calcium excretion in the urine does not indicate a primary hyperparathyroidisme, and as similar cases have been reported, it may be reasonable to relate the extensive decalcification to a general metabolic disorder directly connected with the liver disease.

Summary

A case of neonatal hepatitis with extensive osteomalacia is presented, and the relationship between bone-metabolism and liver disease is discussed.

Hépatite néonatale accompagnée d'ostéomalacie.

Un cas d'hépatite néonatale accompagnée d'une ostéomalacie sévère est rapporté. Le rapport entre le trouble du métabolisme osseux et l'affection hépatique est discuté.

Hepatitis bei einem Neugeborenen mit Osteomalacie.

Ein Fall von Neugeborenen-Hepatitis kombiniert mit ausgedehnter Osteomalacie wird vorgestellt und die Beziehungen zwischen Knochen- und Leberstoffwechsel werden diskutiert.

Hepatitis neonatal con osteomalacia.

Se presenta un caso de hepatitis neonatal con osteomalacia extensa; discutiéndose la relación entre metabolismo óseo y enfermedad hepática.

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Die Kunst der Medizin in China

von SVEND HEINILD

Die chinesische Kunst der Medizin ist nicht die älteste der Welt. Wir haben auf mesopotamischen Tontafeln und ägyptischen Papyri schriftliche Zeugnisse von ärztlicher Kunst, die beinahe 5000 Jahre zurückliegen, also ungefähr 3000 Jahre vor unserer Zeitrechnung. Aber in China treffen wir die älteste, lebende Nation mit einer durch die Zeiten hindurch ständig zusammenhängenden Kultur.

Fig. 1. Orakelknochen aus dem 13. oder 14. Jahrhundert v. Chr. Das Buchstabenzeichen rechts oben ist die alte Form des chinesichen Wortes für scabies.

Fig. 2. Pien Chueh.

Deshalb kann man heute die chinesische medizinische Kunst als die älteste mit bewahrter Tradition bezeichnen, die ihre Wurzeln jedenfalls im 13. oder 14. Jahrhundert vor Cristi Geburt hat. Die ältesten schriftlichen Zeugnisse von der Behandlung menschlicher Krankheiten in China finden wir auf sogenannten „Orakelknochen" aus dem 13. Jahrhundert v. Chr. „The Book of Rites", ein Handbuch der Zeremonien und Gebräuche, geschrieben unter der Chou-Dynastie (12.–15. Jahrh. v. Chr.) behandelt Medizin, Chirurgie, Ernährungslehre, Behandlung von Tieren und verschiedene Formen der ärztlichen Kunst. Aus dieser Periode hat man Gewissheit dafür, dass Furunkel inzidiert und verschiedene Drogen intern angewendet worden sind. Mehr als 300 verschiedene Remedien scheinen damals bekannt gewesen zu sein, und aus dem letzten Jahrhundert vor Christi Geburt liegen die ältesten Rezepte der Welt vor zur Verwendung von Quecksilber und Schwefel bei Behandlung von Hautkrankheiten. Diese letzteren Behand-

angsmethoden kennt man ca. 1000 Jahre später in Arabien und Indien, aber in Europa sind sie erst im 16. Jahrhundert zur Anwendung gekommen.

Schon im 12. Jahrhundert vor Christus werden zwei bestimmte Formen von Patientenbehandlung erwähnt, die Akupunktur und die Moxibustion, die man beide noch heute anwendet.

Bei der *Akupunktur* führt man biegsame Metallnadeln an verschiedenen Stellen des Körpers ein — man führt an, dass es im ganzen ungefähr 300 Punkturstellen gibt — es um „die Funktion des Nervensystems zu regulieren". Man beabsichtigt damit eine Blutentnahme oder Punktur von Hohlräumen. Bei der *Moxibustion* brennt man in einer Art und Weise, die an Tabakrauchen erinnert, zigarrenähnliche Gebilde von Artemisia vulgaris über verschiedenen Stellen der Haut ab, aber man erstrebt nicht, wie ab und zu fehlerhaft angenommen, eine Lädierung oder Verbrennung der Haut selbst. Ebenfalls werden verschiedene Massagensysteme, die auch heute noch angewandt werden, aus dieser Periode erwähnt, und man hat die Gewissheit, dass damals sowohl praktische Ärzte für die Bevölkerung existierten, wie auch Ärzte, die angestellt waren, um die Mitglieder der herrschenden Dynastie im 5. Jahrhundert vor Christus zu behandeln.

Aus dem 5.–4. Jahrhundert vor unserer Zeitrechnung liegt die grösste Erfindung in der Medizin vor, nämlich *Pien Chuehs Beschreibung der Bedeutung des Pulsfühlens*. Auf dieser Basis bildete sich eine umfangreiche medizinische Literatur in China, die die chinesische klinische Medizin für alle Zukunft geprägt hat. Diese Entdeckung wurde im 6. Jahrhundert n. Chr. nach Japan überführt und erreichte erst im 9. Jahrhundert n. Chr. Arabien, wo Avicenna sie im 10. Jahrhundert in seinem „Canon of Medicine" beschreibt.

Pien Chueh war der erste uns bekannte Arzt, der versucht hat, eine Synthese des bestehenden medizinischen Wissens zu schaffen. Er entsagte allen Hexen- und Zauberkünsten und versuchte, eine Krankheitslehre auf anatomischer Basis zu gründen. Seine Hauptgedanken hat er in seinem Werk „Nan Chieng" niedergeschrieben. Aus dem 3.–2. Jahrhundert v. Chr. kennen wir Chang Chungchings „Ching Kuei Yu Han Chieng" (Medizinische Prinzipien), und Huang Ti Nei Ching, ein Handbuch, das durch Jahrhunderte hindurch benutzt worden ist, und das das erste zu sein scheint, das den chinesischen Grundgedanken feststellt, nämlich, dass der menschliche Körper ein integrierender Bestandteil des Universums ist (Mikrokosmus und Makrokosmus). Man hebt hervor, dass es in höherem Masse gilt, Krankheiten vorzubeugen, als diese zu heilen, wenn sie erst entstanden sind.

Als prophylaktische Massnahmen schlägt man vor, ein regelmässiges Leben zu führen, mit passender Ernährung und einer passenden Mischung von Arbeit und Ruhe. Dies erfordert ein ruhiges Herz und einen stillen Sinn.

Im übrigen teilte man die Krankheitsursachen in externe (Kälte, Hitze, Trockenheit, Feuchtigkeit, Wind und Feuer) und interne (Freude, Zorn,

Angst, Begehren, Trauer und Furcht) ein. Unter arabischem Einfluss, auf den ich später zurückkommen werde, ging man im 14. Jahrhundert dazu über, dieses System zu vereinfachen und nur von den „vier Luftarten", Wind, Kälte, Wärme und Feuchtigkeit zu sprechen. Beide Systeme, namentlich aber wohl das erste, können unseren heutigen Hygienikern und Psychosomatikern allerhand zu denken geben. Unter der Han-Dynastie, ungefähr zur Zeit von Christi Geburt, soll die Chirurgie ein hohes Niveau gehabt haben. Hua To führte grosse Unterleibsoperationen aus, und zwar in universeller, von Drogen hervorgerufener Anästhesie.

Im 7.–9. Jahrhundert n. Chr., unter der bekannten Tang-Dynastie, erreichte die Kunst der Medizin ihre Blütezeit in China.

Die erste Ärzteschule der Welt wurde hier nämlich im 7. Jahrhundert errichtet, während die Salernoschule, die erste in Europa, erst 200 Jahre später das Licht der Welt erblickte. Die chinesische Schule hatte ungefähr 350 Studenten. Man hatte Abteilungen für Medizin, Chirurgie, Pädiatrie, Moxibustion, Augen-, Ohren- und Zahnkrankheiten. Ausserdem gab es eine pharmakologische Abteilung. Die Studienzeit betrug 3–7 Jahre. Man kennt in China Krankenhäuser aus dem 5. Jahrhundert, und weitere wurden unter der Tan-Dynastie errichtet. *Materia Medica* enthielt nun 844 verschiedene Medikamente.

Die Zeit zwischen dem 10. und 14. Jahrhundert kann als eine äusserst interessante Epoche bezeichnet werden. Diese Periode ist erstens charakterisiert durch die grossen Invasionen vom Norden her (Tartaren und Mongolen) und die sich daraus ergebende ökonomische und kulturelle Stagnation. Zweitens aber ist sie auch dadurch charakteristisch, dass mit der Zeit, als sich die eindringenden Völker dem chinesichen assimilierten und dessen Gebräuche, Regierungsform, Kultur und Literatur annahmen, ein für damals einzigartiger Kontakt mit der Umwelt eintrat. Besonders ist in dieser Periode eine Wechselwirkung zwischen chinesischer, indischer und arabischer Kultur zu spüren.

Im 13. Jahrhundert arbeiteten Frank Isaiah und John von Montecorvino als Ärzte in Peking. Sie waren somit die ersten, die die westliche Medizin in China einführten. Zu derselben Zeit wurde ebenfalls ein rein arabisches Krankenhaus in Peking gegründet. Unter Kublai Khan war China das grösste Reich, das jemals auf Erden existiert hat. Es erstreckte sich von den Küsten des stillen Ozeans über Indien, durch Sibiriens Steppen bis nach Arabien, den Mittelmeerländern und Osteuropa. Hiermit war der Grund gelegt für nach damaligen Verhältnissen weitverzweigte Handelsverbindungen, und Medizin und Drogen wurden zu wichtigen Exportartikeln.

Aus dem 16. Jahrhundert stammen die Versuche der chinesischen Ärzte, die damals weitverbreiteten Pockenepidemien zu überwinden. Mehr als

50 Lehrbücher sind hierüber geschrieben worden, und das praktische Resultat war, dass man in der Mitte des 16. Jahrhunderts zu einer gewissen Form der Inoculation kam, die darin bestand, dass man in verschiedener Art und Weise Pustelsekret in den Nasenlöchern der Patienten anbrachte, die geimpft werden sollten. Diese Methode benutzte man in China in den folgenden 200 Jahren, und trotz ihrer mangelhaften Resultate bewirkte sie, dass zahlreiche fremde Ärzte, u. a. aus der Türkei, China besuchten. Dort fingen dann die Engländer ihre Studien dieser Methode an (Lady Montague), und auf Grundlage hiervon arbeitete Jenner im Jahre 1798 die noch heute angewandte Kuhpocken-Impfung aus. Unter der Manchu-Dynastie (1644–1911) trat dann die eigentliche Stagnation ein, nicht nur in wirtschaftlicher, sondern auch in kultureller Hinsicht. Der Grund hierzu muss in der wachsenden Furcht vor dem Eindringen der Westeuropäer gesucht werden. Die Portugiesen, die übrigens die Syphilis mit sich brachten, waren schon um 1550 herum nach Macao gekommen. Versuche, westeuropäische Gedankengänge einzuführen, wurden hart bestraft, eventuell sogar mit dem Tode, und so waren z. B. Thomas Bartholins anatomische Werke in dieser Epoche streng verpönt. Man wandte seine Aufmerksamkeit ausschliesslich der klassischen chinesischen Tradition zu, das Volk zog sich in sich zurück, der Fortschritt hörte auf. Die Zeit von dem herostratisch berühmten Opiumkrieg um 1840 bis zum Ausbruch der Revolution im Jahre 1911 ist eine Periode unvergleichlicher Erniedrigung in der Geschichte Chinas.

Nach Kuomintangs Übernahme der Regierungsmacht, unter Chiang Kai Chek in den zwanziger und dreissiger Jahren dieses Jahrhunderts, erstrebte man aufs neue eine Verbindung mit westeuropäischer Zivilisation, aber unter dem Einfluss hiervon betrachtete man gleichzeitig die klassische chinesische Kunst der Medizin als rückständig und unwissenschaftlich und verfolgte sie geradezu. Dies erweckte grosse Animosität in der Bevölkerung, die Zutrauen zu den traditionell ausgebildeten, chinesichen Ärzten hatte.

Wie wird nun die chinesiche Kunst der Medizin, die, wie hier gezeigt, auf Traditionen beruht, die wohl einzigartig in der Welt sind, die aber in der Erniedrigungsperiode dieses grossen, unglücklichen Landes im letzten Jahrhundert (während des „halbkolonialen Zustandes") von Stagnation, jedenfalls in technischer Hinsicht, geprägt ist, den Anforderungen der heutigen Zeit gerecht werden?

Zusammenfassung

Die chinesische Kunst der Medizin beruht noch heute auf einer ununterbrochenen Tradition, die jedenfalls aus dem 14. oder 13. Jahrhundert vor unserer Zeitrechnung stammt. So wird z. B. die Akupunktur und die Moxibustion wie vor 3000 Jahren angewandt. Pien Chueh beschreibt als erster im 5.–4. Jahrhundert v. Chr. die Bedeutung des Pulsfühlens. Erst kriegerisches Zusammentreffen unter der Mongolendynastie im 11.–12. Jahrhundert, später weitverzweigte Handelsverbindungen unter der Ming-Dynastie im 14.–15. Jahrhundert befördern eine eingehende Wechselwirkung zwischen chinesischer, arabischer und europäischer Heilkunde. Auf Grund von Chinas halbkolonialem Zustand im Laufe der letzten 100 Jahre musste das Land die hohe technische Entwicklung der westeuropäischen Medizin entbehren. Diese fehlenden Fortschritte versucht man jetzt nachzuholen.

The Art of Medical Treatment in China.

The Chinese art of treatment depends even to-day on an uninterrupted tradition which may be dated from the 14th or 13th century before Christ. Akupuncture and moxibustion were for instance used 3000 years ago. Pien Chueh is the first author who, in the 5th to the 4th century before Christ, describes the importance of palpation of the pulse. The wars during the Mongolian dynasty in the 11th to 12th century and later the widely extended commercial connections during the Ming Dynasty in the 14th to 15th century and the contact with foreign people they entailed promoted a marked reciprocal exchange between Chinese, Arabic and European medicine. Due to the semi-colonial state of China during the last 100 years the country had to do without the high technical development of West-European medicine. Efforts are being made to recover the ground one has lost.

L'art thérapeutique en Chine.

L'art thérapeutique chinois est encore à l'heure actuelle sous l'influence d'une tradition ininterrompue, qui remonte au XIV^{e} ou XIII^{e} siècle avant J. C. Ainsi, l'acuponcture et la moxibustion sont en usage depuis plus de 3000 ans. Pien Chueh fut au V^{e} ou IV^{e} siècle avant J. C., le premier auteur qui décrivit l'importance de la prise du pouls. Les guerres qui survinrent durant le règne de la dynastie mongolienne au cours des XI^{e} et XII^{e} siècles, et par la suite l'augmentation considérable des échanges commerciaux sous la dynastie des Mings au cours des XIV^{e} et XV^{e} siècles, ainsi que les contacts avec d'autres peuples étrangers, entrainèrent à cette époque des échanges entre les méthodes thérapeutiques alors en pratique dans les arts médicaux chinois, arabes et européens. Puis, l'état semi-colonial dans lequel la Chine resta au cours des 100 dernières années, fit que ce pays ne suivit pas le développement élévé de la médecine dans les pays Ouest-Européens. Il y a là une lacune que ce pays s'efforce maintenant de combler.

El arte de curar en China.

El arte terapéutico chino se halla todavía bajo la influencia de una tradición que, ininterrumpidamente, se remonta a los siglos XIV o XIII antes de Cristo. La acupuntura y la moxibustión por ejemplo se usan desde hace mas de 3000 años. Alrededor del V° o IV° siglo antes de Cristo, Pien Chueh describió por primera vez la importancia

del control del pulso. Las guerras acaecidas durante las dinastías mongolianas (siglos XI y XII), el aumento considerable de los intercambios comerciales durante las dinastías Ming (siglos XIV y XV) así como los contactos con otros pueblos extranjeros significaron en esos siglos un intercambio entre los métodos terapéuticos entonces en práctica entre los médicos chinos, árabes y europeos. El estado semi-colonial que dominó la China durante los últimos 100 años hizo que este país no siguiera el progreso experimentado por la medicina en los paises de Europa occidental. Hay una laguna que el país se esfuerza ahora por llenar.

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Kinderabteilung
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From Sundby Hospital, Children's Department, Copenhagen (Head: C. FRIDERICHSEN, Children's Hospital Martinsvej, Copenhagen (Head: E. W. FLENSBORG), Copenhagen County Hospital, Children's Department, Hellerup (Head: P. W. BRÆSTRUP), St. Josephs Hospital, Children's Department (Head: EJN. LENSTRUP) and Children's Hospital on Fuglebakken, Copenhagen (Head: A. ROTHE-MEYER)

5 hospitals in Copenhagen

Pneumonia in Children

Treatment with one Single Injection of Procaine Penicillin Compared with Continuous Treatment[1]

by TORBEN JERSILD, JOHS. MELCHIOR, IB BOESEN, HOLGER BUCH, SV. E. NIELSEN and ERIK WAMBERG

In 1940 Platt reported favorable results with sulfapyridine given as a single large dose in pneumonia in children. Friderichsen and Søbye published the results of single-dose sulfathiazole treatment in pneumonia in children in 1941. This therapy has since proved its value and has, to a large extent, been the preferred method of treatment.

After the advent of penicillin, the sulfonamides were pushed into the background because of the lower toxicity of penicillin.

After the favorable results with single-dose sulfa treatment, it was natural to try if a single large injection of penicillin would be as effective as the continuous therapy. In 1949 the treatment of pneumonia with a single large dose of penicillin was therefore begun in the Children's Department of Sundby Hospital. The preliminary results were reported to the Danish Pediatric Society in May, 1950 (Friderichsen, Jersild and Mehlsen).

The preliminary results were favorable since they showed that the single dose penicillin treatment was comparable to five day continuous penicillin therapy. A cooperative study was therefore started among five children's departments in Copenhagen.

Own Series

From April 1951 until April 1953, 1011 children with pneumonia were admitted to the above named children's departments. They were treated

[1] This work was aided by a grant from King Christian X' Foundation, Copenhagen City Dept. II and from NOVO, Therapeutisk Laboratorium a/s, Copenhagen. The statistical calculations were performed by Henry F. Holm, Copenhagen.

according to the following plan: Children admitted on an even date received a single dose of procaine penicillin; children admitted on an odd date were treated with penicillin for five days. The dosage is shown in Table 1.

TABLE 1

Penicillin dosage in the two treatment groups.

Age	Single dose (procaine penicillin)	Penicillin for 5 days
0–11 mths.	200,000 I.U. i.m.	60,000 I.U. × 2 daily
1–5 years	300,000 I.U. i.m.	90,000 I.U. × 2 daily
6–11 years	400,000 I.U. i.m.	120,000 I.U. × 2 daily

Of the 1011 children, 429 had received chemotherapy before admission and were therefore excluded from the material. Eleven patients were so severely ill on admission that treatment with penicillin alone was considered insufficient, and broad-spectrum antibiotics were therefore given immediately. These 11 patients are not included in the report.

After these exclusions the final series of primary penicillin-treated patients includes 571 children. There were no deaths. Two hundred and forty-five were treated with a single large penicillin dose, and 323 with continuous penicillin injections (Table 2).

TABLE 2

Distribution of treatment groups in the various departments.

Hospital	Single dose		Continuous treatment	
	Number	%	Number	%
Sundby	82	33	67	21
Fuglebakken	15	6	30	9
Martinsvej	74	30	122	38
St. Joseph's	25	10	26	8
County Hospital . . .	52	21	78	24
Total	248	100	323	100

The similarity of the two groups in regard to age, clinical condition at the onset of treatment, together with the results of the most important findings are shown in Tables 3, 4, and 5.

The temperature, pulse and respiration at the beginning of therapy did not differ significantly in the two groups. In 74% of the single-dose treated

patients, the symptoms of illness had appeared three days or less before penicillin therapy. The corresponding figure for the continuously treated group was 76%.

Accompanying illnesses are distributed equally among the two groups – thus congenital heart disease was found in two patients in each group; 1 patients had rickets in the single-dose group and 16 in the continuous-treatment group. Dyspepsia was found in 13 patients, 6 in the single dose group and 7 in the continuously treated one.

TABLE 3

Age distribution in the two groups.

Age	Single dose %	Continuous treatment %
0–5 mths.	25	25
6–11 mths.	19	19
1–2 yrs.	25	29
3–5 yrs.	26	18
over 6 yrs.	5	9

TABLE 4

Clinical condition at the beginning of therapy.

	Single dose %	Continuous treatment %
Severely ill	10	9
Moderately ill	55	54
Slightly ill	35	37

Of the 571 patients, 182 in the single-dose group and 239 in the continuous group, had a temperature over 38°C on admission (Table 6).

Table 6 shows that the temperature became normal (below 37.2/37.5) in less than 24 hours in 52% of patients in the single dose group, while only 38% of the continuously treated children became afebrile. This difference is statistically significant. Forty-eight hours after the beginning of penicillin therapy, only 24% in the single dose group were still febrile against 36% in the continuously treated group.

Secondary rise in temperature, by which is meant fever after the end of the penicillin treatment, occurred in 25% of patients in both groups.

TABLE 5

The most important examinations in the two groups.

Examination	Performed in % of		Result	In % of performed examinations in	
	Single dose	Contin. treatment		Single dose	Contin. treatment
X-ray of lungs . . .	93	96	definite infiltration	39	36
			doubtful infiltration	20	23
Throat culture . . .	57	52	positive	37	33
Cold agglutinin titer .	76	71	titer above 16	4	5
Sed. rate (micro) . .	98	97	10–20 mm/hr	35	47
			above 20 mm/hr	39	30
Hb. % (Sicca)	100	100	less than 85 %	35	35
Leukocyte count . .	88	92	above 10,000	59	62

TABLE 6

The course of the fever after onset of therapy in the 421 patients who had a temperature above 38°C.

	Single dose %	Continuous %
Less than 12 hours . . .	20	15
12–24 hours	32	23
25–48 hours	24	26
More than 48 hours . . .	24	36

Repeated single injections were given to 8 of the 248 patients in the single-dose group. In this connection, it is of interest to note that on one occasion repeat therapy was necessary due to consecutive pneumonias which appeared first in one lung and then in the other. In the continuously treated group, it has been necessary to repeat the series of penicillin injections in 13 of the 323 patients.

More serious complications, such as empyema or lung abscess, did not occur in our series. Suppurative otitis media developed in 11% of patients in the single-dose group against 16% in the continuous-treatment group. Acute tonsillitis appeared in 4 and 5% of patients, respectively.

Conclusion

This investigation has demonstrated that a single procaine-penicillin injection is equally effective in the treatment of pneumonia as several daily

injections given for five days. The single injection is easier to administer and more agreeable with the child. It is especially fitting for home treatment.

If there is no therapeutic response within 48 hours, diagnosis and therapy should be reconsidered.

April 51 – 53

Summary

Five hundred and seventy-one children, admitted with pneumonia over a two-year period to five children's departments in Copenhagen, were treated alternatively with one single injection of procaine penicillin or with continuous dosage for five days. Two hundred and forty-eight received one single dose and 323 continuous treatment. The results of the two treatments are the same; howevever, the patients treated with one single injection attained a quicker temperature fall than the patients treated with continuous dosage.

La pneumonie dans l'enfance. Traitement avec une seule injection de pénicilline-procaine comparé au traitement continu.

571 enfants avec pneumonie qui étaient entrés pendant une période de deux ans dans cinq différents services pour enfants à Copenhague ont été traités alternativement avec une seule injection de pénicilline-procaine ou avec des doses continues pendant cinq jours. 248 recevaient une seule dose et 323 un traitement continu. Les resultats des deux traitements sont les mêmes; les patients qui recevaient une seule injection montraient pourtant une régression de température plus rapide que ceux avec traitement continu.

Pneumonie bei Kindern. Behandlung mit einer einzigen Injektion Procain-Penicillin, verglichen mit kontinuierlicher Therapie.

571 Kinder, die in einer Zeitspanne von zwei Jahren in fünf Kinderkliniken Kopenhagens mit Pneumonie aufgenommen wurden, wurden abwechselnd mit einer einzigen Injektion Procain-Penicillin oder mit fortlaufender Dosierung fünf Tage lang behandelt. 248 erhielten eine einzige Dosis und 323 kontinuierliche Behandlung. Die Ergebnisse der beiden Behandlungsarten waren dieselben, doch erreichten die Patienten mit einer Injektion einen schnelleren Temperaturabfall als die Kinder, die mit fortlaufender Dosierung behandelt worden waren.

Neumonia en niños. Comparación del tratamiento con inyección única de penicilina procaína y tratamiento continuo.

En 5 diferentes servicios de pediatría de Copenhague fueron admitidos, en un período de dos años, 571 niños afectos de neumonia. Estos fueron tratados alternativamente con una única inyección de penicilina procaína o con dosis continuas durante 5 días. 248 recibieron una dosis única y 323 tratamiento continuo. Los resultados fueron iguales en ambos grupos; sin embargo, los pacientes tratados con penicilina procaína presentaron una caída de la temperatura mas rápida que los del otro grupo.

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Acute Hepatitis with Fatal Outcome in a Two-year-old Child

by SVEND ERIK NIELSEN

Hepatitis in childhood is generally considered a benign disease, practically always ending in complete cure. In rare cases, however, it may entail degenerative changes of the hepatic parenchyma. Such changes may develop slowly, so that symptoms of cirrhosis do not become manifest until months or years later. Craig, Gellis & Yi-Yung-Hsia have reported 8 cases of this nature seen during the period 1924–1953 in the Children's Medical Center in Boston. The onset of the degenerative changes may, however, also be more stormy, in direct connection with the hepatitis. If so, the patients rapidly develop insufficiency of the liver, ending in hepatic coma and death.

The latter is exemplified in the following case:

A 2-year-old boy, born of healthy parents as No. 2 of 2 siblings, had thrived well and been in perfect health until the present illness.

On Sept. 24 his mother noticed incipient yellow discolouration of his skin. His urine was dark and his faeces light. In addition, his appetite was poor, but there were no other complaints, especially no vomiting, and the temperature was normal.

Two days later he was admitted to the Paediatric Department of the St. Joseph Hospital. He was not debilitated, but physical examination revealed moderate jaundice of the skin and sclerae. The edge of the liver was palpable about 1 cm below the costal margin. The spleen did not appear to be enlarged. His temperature was 37.4°C. Laboratory tests disclosed Hb. 101 %, E.S.R. 6 mm, icterus index 72, thymol turbidity test and Takata-Ara negative. The urine was very dark and the stools pale, though not entirely decoloured.

The patient was treated with bed rest and a low fat, high carbohydrate diet.

During the first week, his condition was fairly good, although his appetite was poor. He was running a temperature of about 38°C. The stools were thin, mushy, and gradually completely colourless. The jaundice deepened and the hepatomegaly increased, the liver reaching a hand's breadth below the costal border at the end of two weeks.

Three weeks after admission the laboratory values were as follows: Hb. 98 %, E.S.R. 5 mm, icterus index 108, thymol turbidity test and Takata-Ara still negative, white blood count and differential count normal, serum protein 5.8 %, fragility of red cells 0.38–0.26. Now his condition had deteriorated, his abdomen was slightly distended, but there were no definite signs of ascites. No oedema.

Treatment with aureomycin, 100 mg 4 times daily, was attempted for one week. The patient, however, went downhill and the jaundice deepened. Four weeks after

admission he exhibited increasing somnolence. At this juncture the Hb. was 80 %, E.S.R. 2 mm, icterus index 156, thymol turbidity test (+), Takata-Ara +, serum proteins 3.7 % (alb. 2.9, glob. 0.8), alkaline phosphatases 18.2 units (5.4–16.1 being normal for the age), prothrombin time 118 sec. (norm. 19).

Now, there were distinct oedema and ascites. The liver seemed to have decreased somewhat in size, and the spleen was impalpable.

On Oct. 26 he was entirely comatose. Blood transfusion and subcutaneous infusion of glucose failed to arouse him, and on the next day he died—a little more than one month after the onset.

Post-mortem findings: Liver 18 × 14 × 5 cm. Smooth surface. A bright yellowish-brown on the surface and cut surface. Cut surface completely uniform and structureless.

Spleen: 10 × 6 × 4 cm. Dark bluish-red on the surface. Firm consistency.

Oesophagus: Slightly dilated veins at the cardia.

In the peritoneum 200 ml of an icteric, serous fluid.

Post-mortem diagnoses: Subacute hepatitis, mild ascites, mild oesophageal varices, moderate splenic hyperplasia.

Micr. exam. of hepatic tissue: No normal liver tissue in the sections examined. The tissue consists of a network of connective tissue the meshes of which show the remains of highly changed liver cells and numerous small biliary ducts. Micr. diagn.: Severe hepatic cirrhosis.

Pancreas: No particular changes.

Kidneys: No glomerular changes. In the medulla numerous small areas of dilated, blood-filled capillaries. Micr. diagn.: Medullary hyperaemia.

Spleen: Pronounced congestion with parenchymal haemorrhage.

Summary

In connection with acute hepatitis a two-year-old boy developed insufficiency of the liver ending in hepatic coma and death.

Hépatite aiguë entraînant une issue fatale chez un enfant de deux ans.

Par suite d'une hépatite aiguë, un enfant de deux ans développa une grave insuffisance du foie, qui entraîna la mort dans un tableau de coma hépatique.

Akute Hepatitis mit letalem Ausgang bei einem zweijährigen Kind.

In Zusammenhang mit einer akuten Hepatitis entwickelte sich bei einem zwei Jahre alten Jungen eine Insuffizienz der Leber, die zum Leberkoma und Tod führte.

Hepatitis aguda con desenlace fatal en un niño de 2 años.

Un niño de dos años desarrolló un coma hepático fatal a consecuencia de una hepatitis aguda.

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From The University Pediatric Clinic and The University Psychiatric Laboratory, Rigshospital, Copenhagen

Combined Lesions of Basal Ganglia, Medulla Oblongata, and Spinal Cord in a 10 Year Old Boy

by ERNA CHRISTENSEN, J. MELCHIOR and P. FLUM

In the following we will describe a case of progressive nervous disease resembling cerebral palsy and torsion spasm with unusual pathoanatomical lesions.

Case Report

Boy F. D. (case record no 182/55, Rigshospital, Children's Department).

Family history. His father died 42 years old from cancer pancreatis. A 37 year old sister of his father, still living, is mentally retarded, has diabetes mellitus and looks as if she has myxoedema; she has no spasticity or athetosis.

Siblings. His older brother died 7 months old from whooping-cough. His younger half-sister is healthy.

Pregnancy. The mother told that she had hypertension, and was nervous during this pregnancy.

Birth. He was born two weeks too early without complications. No asphyxia, no jaundice, birth weight 3100 g, length 51 cm. Vitamin K was not given.

Early development. According to his mother he developed normally until the age of two. He could sit alone 6 months old, and walk alone 11 months old. The family doctor and a relative feel that his gait was never quite normal: his right leg was unsteady and he fell more than normally. At the age of 2½ the family doctor found a right hemiplegia which seemed to improve for some months but became worse after a minor accident followed by vomiting and fibrillary twitchings round his mouth and eyes. When he was 3 years old, he could no longer walk without support, and he was admitted to the Neurosurgical Department of the Rigshospital (case record no. 01004/48).[1]

Physical examination at the age of 3 years. Normal appearance and bodily proportions. Head circumference 52 cm. Eyegrounds normal. Slight paresis of oral part of facialis. Right spastic hemiplegia, most pronounced in the leg. Tendon reflexes hyperactive on the right side. Babinski positive. Hemiplegic, unsteady gait. Speech slow and dysarthric. Skin sensibility normal. Ventriculography normal (Fig. 1).

Course from the age of 3 to 6 years. There was a steady progression of symptoms and from he was 5 years old he could no longer grasp or hold things, could not wash, feed, or dress himself, his left hand being worse than his right. His speech became more and more difficult to understand.

[1] We wish to thank Professor E. Busch for his kind permission to make use of the case record and encephalogram.

Fig. 1. Ventriculogram at the age of 3 years demonstrating normal anterior horns.

At the age of 6 $^{9}/_{12}$ years he was admitted to the Children's Department, Rigshospital, and stayed there until his death.

Physical examination at the age of 6 $^{9}/_{12}$ years. His intelligence was normal and he showed a vivid interest in his surroundings and had a good sense of humour. Speech: slow, difficult pronunciation, difficult to understand. No definite facial paresis. No nystagmus or strabismus. Eyegrounds normal. Muscular tonus: there is a continuous resistance to passive movements all over. Some degree of muscular atrophy. His left elbow is flexed, the left hand is closed and in dorsal flexion, and the forearm is kept against his chest. He moves his right arm with extended elbow (Fig. 2). The finger-finger test is performed rather well. Adductor spasm of both hips. Flexion contracture of the right knee and extensor spasm of the left knee. No equinus, the left foot being kept in dorsal flexion. Tendon reflexes on the upper extremities exaggerated. Knee jerk hyperactive and can be elicited all over from left tibia. No ancle clonus. Abdominal reflexes normal. The toes of the right foot are kept in dorsal extension but there is a flexor response on both sides.

Locomotion: Cannot crawl, stand or walk. He cannot sit without support.

Involuntary movements. No real athetosis but poor coordination and difficulties in reaching for objects.

A preliminary diagnosis was made of degenerative, progressive brain lesion with severe rigidity, no or slight athetosis, severe disturbance of speech, probably unimpaired intelligence.

Fig. 2. Patient 6 $^{9}/_{12}$ years old, during a bad period.

Course from the age of 6 $^{9}/_{12}$ years until death at the age of 10 $^{7}/_{12}$ years. On the whole his symptoms showed a steady and slow progression though periods lasting from weeks to months of slight improvements alternated with relapses (Fig. 3). In certain periods he could eat bread without assistance, and carry out easy needlework and home art with the help of an occupational therapist and even use a spoon. He liked speech therapy and ordinary schoolwork, and he was good in arithmetic. He could read but not pronounce the words properly. His memory was good; for example he was asked to name a word which was spelt the same way forwards and backwards and the could immediately mention an uncommon word with 5 letters, which most adults would not have found ("kajak"). His emotional stability decreased, and even if he always retained his sense of humour, he became increasingly depressed.

He could control his bowel movement and urination until three years before death.

When he was 8 $^{4}/_{12}$ years old a divergent strabismus had developed and he had a squint operation 11 months later. At the age of 10 years the adduction contracture of his hips had caused a bilateral subluxation, and besides there was now a flexion contracture of both knees, most pronounced on the left side. The contracture of the knees were corrected surgically at The Orthopedic Hospital in Copenhagen. As before, there was no equinus.

At the age of 10 $^{4}/_{12}$ years he had a sudden attack of cyanosis and collapse at 3 o'clock in the morning; there was no fever, no convulsion, and he soon recovered after oxygen therapy. He never had convulsions.

On several occasions his relapses were initiated by a temperature of 38–39°C for a few days. Frequently no physical signs were found at those occasions.

Physical examination at the age of 10 years. He was small and slim, length 119 cm, weight 20 kg. Head circumference 53 cm. He was always pale in spite of normal haemoglobin value. The muscles were reduced in size all over.

When kept in walking position he could only make slight movements of his hips, but he could neither bend his knees nor move his feet; he could not sit, stand or walk.

When he was lying quietly in his bed, without intention to move, the arms were most often relaxed but the legs were always stiff. When he tried to do something with his arms, or was asked to take pains to do it, they also turned rigid. When he wanted to grasp something, he did it with extended elbow and the hand in dorsal flexion. When he was asked to flex his fingers, he made a flexion in the metacarpophalangeal joints but kept the fingers extended. He could carry out voluntary movements

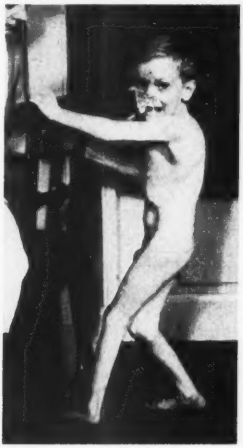

Fig. 3. Patient 7 $^{5}/_{12}$ years old, during a good period.

with his hands. When he was sewing he could hit the right place with the needle, but he did so with slow and interrupted movements. When he tried to move one arm the other arm would often move slowly upwards above his head and on certain occasions such as emotional stress, loud noises, or when he would protect himself from falling, there would occur sudden incoordinated mass movements, which were not athetotic but due to the rigidity and poor coordination they had a certain resemblance to the movements described as torsion spasm. There were no spontaneous hyperkinetic movements such as tremor, jerk, twitching or writhing. (Film records have been taken twice.)

When he was emotional balanced his facial expression was quiet, but when he started talking, or when he was emotionally upset his facial movements would change to grimaces. He tried to assist his difficult chewing with tongue movements. He could swallow fluids without difficulty, but not solid food; he had to eat slowly and often with his head kept backwards, and his dinner would usually last for one hour.

His speech was hard to understand. He could only say a few words fairly clear and only the nurses, who knew him well, were able to understand him.

Vision and hearing normal.

Tendon reflexes of the upper extremities hyperactive. Knee jerk could not be examined because of the stiffness. Plantar reflexes atypical. Pain sensation normal.

Laboratory examinations during this period (6 $^{9}/_{12}$ years old to death). Encephalograms at the age of 6 $^{9}/_{12}$ years show some dilatation of the lateral ventricles compared with those from the age of 3 years. Later encephalograms at the age of 9 years showed a pronounced dilatation of the lateral ventricles (Fig. 4).

Electroencephalograms from the age of 6 years to 10 years were normal on 4 occasions, the last examination being performed some time after the above mentioned attack of cyanosis.

Eyegrounds normal on several occasions.

Wassermann negative. Sabin-Feldman test (dye-test) and complement fixation test for toxoplasmosis both negative. Glutaminic acid of serum normal. Urin normal. Tuberculin test negative. Sedimentation rate and white blood count at normal levels,

Fig. 4. Encephalogram at the age of 9 years. Symmetrical and marked dilatation of both anterior horns.

Fig. 4 a. Patient 10 $^{6}/_{12}$ years old, a few weeks before his death.

except during periods of upper respiratory infections. Roentgen examinations of skull and cervical columna showed no abnormities; during his last year there was halisteresis of the long bones of the legs.

Treatment. Besides the above mentioned squint operation and orthopedic surgical procedures he had exercises, nightsplints, occupational therapy, speech therapy, and school training. Furthermore he was given antispasmodic drugs (parpanit, peragit, rigidyl) with doubtful effect. The small improvements that appeared periodically could perhaps to some extent be accounted for by these therapeutic measures which on the whole could not prevent the progress of the disease.

His death occurred suddenly and unexpected. Without previous symptoms he was found one morning to have fever and rapid respiration. Signs of infection could not be found. His condition grew worse in a few hours, the respiration became irregular, of Cheyne-Stokes type, the temperature rose above 41°C, and he died eight hours after the onset of symptoms.

Clinical Summary

A boy 2 years old develops a slight right-sided, spastic hemiplegia after a normal birth, and normal motor- and mental development. At the age of 3 his hemiplegia has progressed so much that he can hardly walk, and his speech is affected. During the following 3 years all four extremities became involved, and the speech became more dysarthric. During the last 4 years the disease shows further progression. He is unable to walk. He develops divergent strabismus, adduction contracture of the hips, and flexion contracture of the knees. During this stage he has fever for short periods without known reason. At the age of $10\,^{7}/_{12}$ years he suddenly has hyperpyrexia and Cheyne-Stokes respiration and dies within eight hours. His intelligence was unimpaired until his death and in spite of increasing difficulties, he remained able to speak a little, and to perform voluntary movements of his head and arms. His arm and hand movements were stiff, slow, abrupt, badly coordinated, and even if they had a certain resemblance to torsion spasm they could not be described as such since there were no spontaneous involuntary hyperkinetic movements.

Encephalograms were made three times: At the age of 3 years it was normal; at the age of 6 years a slight dilatation of the lateral ventricles was found, and at the age of 9 years the dilatation was pronounced (corresponding to a progressive atrophy of the basal ganglia (see below)).

Autopsy

At post-mortem examination abnormalities were only found in the central nervous system. The liver was normal macroscopically and microscopically. The lungs were normal on macroscopic examination; microscopically a slight hyperemia, but no signs of inflammation were found.

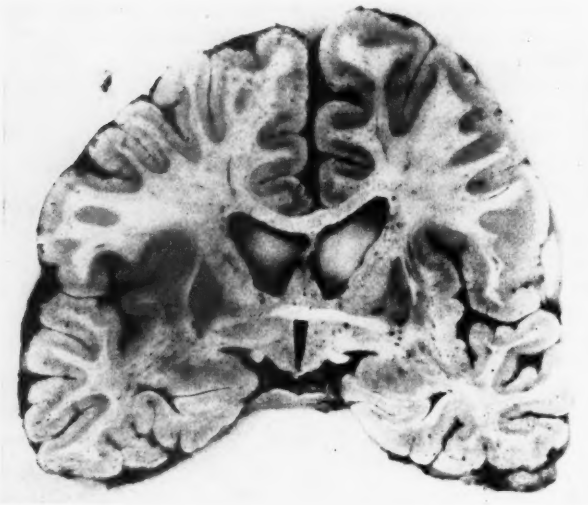

Fig. 5. Coronal section of brain at the anterior commissure demonstrating the ventricular dilatation, atrophy of nuclei caudati and necrosis of both putamina.

Macroscopical examination of the brain

Brain weight after formalin fixation was 1475 g. The brain surface and the cerebral vessels did not show any changes. Coronal sections revealed symmetrical, moderate dilatation of the lateral ventricles, due to macroscopical visible atrophy of both caudate nuclei. However, the most striking abnormality was a symmetrical, sharply outlined necrosis and cystic degeneration of both putamina (Fig. 5), while the internal capsules, the globus pallidus, thalamus, and hypothalamus on both sides did not show any gross abnormalities. Also mesencephalon and pons were normal at macroscopical examination, while there was a symmetrical, brownish discoloration in the posterior half of medulla oblongata. Cerebellum and the spinal cord did not reveal any macroscopical changes.

Histological examination of the brain

Cortex. In the cortical grey matter there is a slight scattered atrophy of the ganglion cells with surrounding glial proliferation.

The *white matter* of the hemispheres, the *meninges*, and the *vessels* are normal.

The *caudate nuclei* show severe atrophy and degeneration of all ganglion cells with complete disappearance of some of the cells. Both the myelin sheaths and the axis-cylinders are destroyed (Fig. 6). The tissue consists of reticular fibrous astrocytes and vessels; the walls of the arterioles are hyalinized and thickened, and the lumina are narrowed. The process is sharply limited but in the delineation zone "gemästete" astrocytes can be seen in between remnants of myelin sheaths. Only in the basal and lateral parts of the caudate nuclei a zone of preserved normal ganglion cells and white matter can be seen.

Fig. 6. Corpus striatum. Atrophic nucleus caudatus and putamen with degeneration of ganglion cells and myelin sheaths. Normal capsula interna, capsula externa, commissura anterior and slight affection of the lateral zone of globus pallidus. Mallory's aniline blue orange-G (× 5.5).

Putamina are completely degenerated symmetrically, (Fig. 6) consisting of reticular glial tissue with cavity formation; the arterioles show thickening and hyalinization (Fig. 7). In the periphery of the sharply limited process new vessels are seen. A fresh perivascular focal process with accumulation of scavenger cells, beginning glial proliferation, and formation of new vessels is found in the basal, medial part of the left putamen extending into the lateral part of globus pallidus.

Globus pallidus. As described above a fresh perivascular focal degeneration is seen in the lateral upper part of the left globus pallidus continuing in a focal scar formation consisting of glial cells and hyalinized vessels. Other examined parts of the right and left globus pallidus were normal. Turnbulls stain did not show increased amounts of iron.

Thalamus. A small focus of perivascular degeneration, histological identical with that in globus pallidus, was found in the left thalamus. Otherwise the microscopical findings were normal.

Substantia nigra. The mesencephalic part shows hyperemia and some degeneration of the pigmented nerve cells, slight glial proliferation, and beginning degeneration of the myelin sheaths.

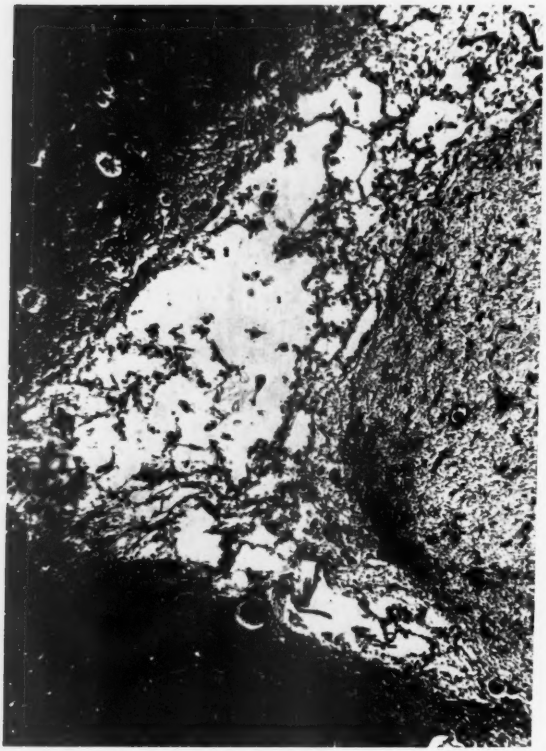

Fig. 7. Lower and medial part of putamen with cystic degeneration, glial proliferation and hyalinized thickened walls of the arterioles. The internal capsule is normal. Weil's myelin stain (× 170).

The *hypothalamic* nuclei, the *subthalamic* nuclei, and the *red* nuclei are histologically normal.

The *dentate* nuclei and *cerebellum* as a whole contain normal nerve cells, myelin sheaths and vessels.

Both *inferior oliva* show fresh degeneration, which was much more severe on the one side (Fig. 8) where the whole nucleus is replaced by scavenger cells, slight glial proliferation, formation of new vessels, hyperaemia and oedema.

The *reticular substance* of medulla oblongata are on both sides completely degenerated (Fig. 9) and the process here seems to be of the same age as the above described fresh foci in globus pallidus, thalamus and inferior oliva (Fig. 10). In the caudal part of the *medulla oblongata* the processes are more widespread (Fig. 8) affecting the spinal trigeminal roots, the dorsal motor nuclei of the vagal nerves, the nuclei ambigui and the hypoglossal nuclei.

The *internal capsules* do not show any abnormalities apart from a small focus of glial proliferation between the lateral part of the left caudate nucleus and putamen.

The *external capsules*, *claustrum*, *insula*, *pyramidal tracts*, and *lemnisci* are normal on both sides.

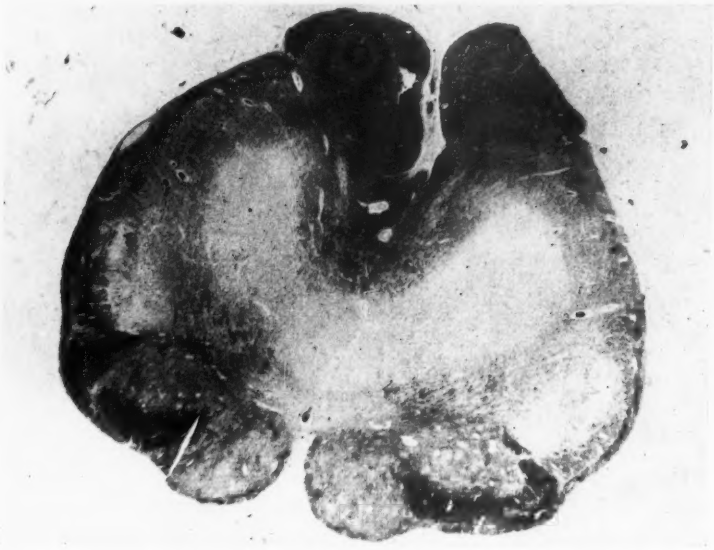

Fig. 8. Lower part of medulla oblongata with widespread degeneration. Weil's myelin stain (× 5.5).

Fig. 9. Medulla oblongata with symmetrical degeneration of the reticular substance. Weil's myelin stain. (× 5.5).

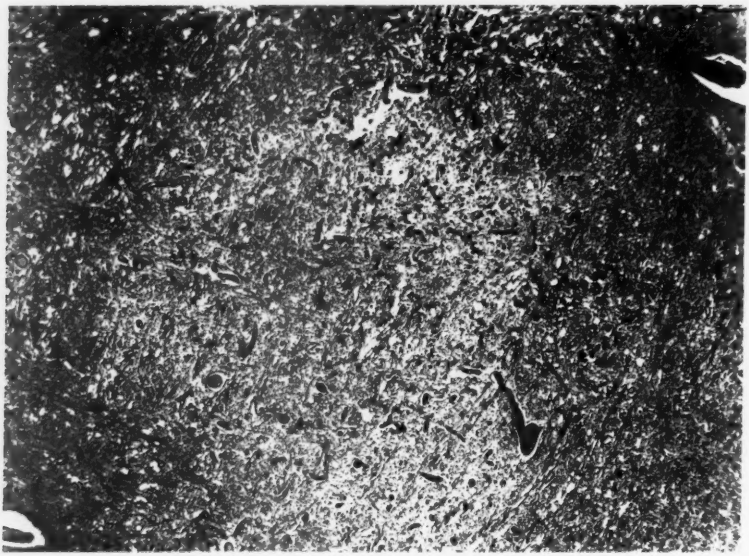

Fig. 10. Fresh degeneration in the reticular substance. Hyperemia, slight degeneration of myelin, lipoidcontaining scavengercells, beginning glial proliferation, but normal vessels. Mallory's aniline blue orange-G stain (× 170).

The spinal cord. In the cervical part the whole of the grey matter is destroyed by a fresh degenerative process; only a few degenerated anterior horn cells are left. The white matter is normal. In the thoracic part the grey matter is moderately degenerated, and in the lumbar part the abnormal findings are reduced to slight swelling of the nerve cells most in the sidehorn and posterior horn.

Concerning the *vessels* it has to be mentioned that there are proliferation of new vessels in the youngest foci, but here the original vessels do not show any other changes than dilatation. The hyalinization and thickening of the walls which are found in the older processes must be considered as a secondary phenomenon.

Signs of inflammation or thrombosis can be seen nowhere in the examined parts of the central nervous system.

Pathoanatomical Summary

We are dealing with a progressive, mostly symmetrical, degeneration of the caudate nuclei, putamina, substantia nigra, the reticular substances, olivas, some of the cranial nerve nuclei in medulla oblongata, and in the grey substance of the spinal cord, especially of the cervical part.

Besides, degeneration is found in the left globus pallidus and the left thalamus.

The pathological process in nucleus caudatus and putamen consists in cystic degeneration and glial scar formation; in globus pallidus both a fresh and an old focal process is found. The processes in medulla oblongata are fresh and characterized by hyperaemia, oedematous glial cells, degeneration of the nerve cells and degeneration of the white matter of the reticular substance. In the grey matter of the spinal cord similar fresh processes are found of decreasing intensity from the cervical to the lumbar part. The nerve cells of the cortical grey matter show only slight chronical degeneration with satellitosis.

In the internal capsule only a small glial scar was found on the left side.

Discussion

A comparison of our case with established syndromes of similar or related nature must include clinical as well as pathoanatomical data, the clinical entities being characterized more or less by familial occurrence and heredity, age, clinical course and pathoanatomical findings.

It is a well-known fact that lesions of the basal ganglia will often produce clinical symptoms consisting in alterations of muscle tonus and various types of hyperkinesia. A comparison of different forms of hyperkinesia is difficult because different names are sometimes used to describe the same phenomenon. Furthermore the abnormal movements are not always described in detail, whether they are slow or fast, localized to proximal or distal joints and whether they are really spontaneous or must be considered as resulting from abnormal movement patterns combined with associated movements. The difficulties in comparing a given case with descriptions from the literature is furthermore increased by the fact that pathoanatomical pictures (e.g. état marbré, état fibreux, état dysmyélinique) (20, 55, 56, 57) have been adopted in the clinical terminology (22).

As the lesions in our case are localized to the basal ganglia we can exclude such progressive diseases of the central nervous system in children which leave these structures intact i.e. Schilder's disease, diffuse sclerosis, Friedreich's ataxia, multiple sclerosis and Alper's diffuse poliodystrophy (7, 9).

Some of the recognized syndromes of the basal ganglia, more or less resembling our case, will be discussed below.

Huntington's chorea (14, 26, 40, 54, 57) is characterized by familial occurrence, onset of symptoms after the third decade, and by lesions of the cortical grey matter, causing dementia.

Hepato-lenticular degeneration (*Wilson*) (19, 52, 57, 61) most often occurs between the age of 15–25 years. The symptoms are tremor or athetosis, mask face, salivation, dysarthria, forced laughter and weeping. The lesions

of the basal ganglia are mainly localized to the putamina; both liver cirrhosis and Kayser-Fleischer's ring are obligate symptoms.

Kernicterus (5, 16, 28, 31, 49, 58, 66). The clinical symptoms of cases of kernicterus surviving the neonatal period are well known, but only few brain autopsies have been reported. The most frequent findings seem to be degeneration of globus pallidus, nucleus subthalamicus (Luys), cornu ammonis, fascia dentata and putamen. Our patient had no neonatal jaundice and no athetosis and the post-mortem examination differed from the above mentioned findings.

Cerebral palsy. If cerebral palsy is defined as conditions due to cerebral lesions, acquired once and for all during the perinatal period, and if from brain autopsies of such cases those are selected which show predominantly lesions of the basal ganglia, it will be seen that these cases clinically are characterized by rigidity and sometimes also by hyperkinesia. These lesions of the basal ganglia may be caused by various related or nonrelated factors: prematurity (18, 64), asphyxia (30, 37), hemorrhagic diathesis (15, 43, 44, 46), and bleedings from venae terminales caused by venous stasis (3, 47, 48) or intrafetal variations of blood pressure (45). In order to compare our case with cerebral palsy cases it is unnecessary to take into consideration the great number of autopsies (33, 38) showing severe macroscopical damages of the hemispheres, thalamus and the basal ganglia.

In the literature we have only found four reports (10, 37, 41, 57) in which the pathology was essentially localized to the basal ganglia and in which symptoms originated from birth. The symptoms of these four patients were stationary and of long duration, the age of death being from 25 to 74 years. They all show spasticity and rigidity, three had athetosis and none had tremor.

Isolated lesions of globus pallidus were found in one case and combined lesions of caudatus, putamen and globus pallidus were found in three cases. Cortex cerebri was normal microscopically in every case.

Our case thus differs from this group with regard to birth history, course and post-mortem findings.

Basal ganglia lesions characterized by late onset of symptoms (after the age of 20) not belonging to the other groups mentioned. We have found nine cases recorded in the literature, of which one had hemiballismus (hemichorea) and eight had progressive choreo-athetosis (senile chorea).

The patient having hemiballismus (8) was a 69 year old woman who died 6 days after onset of characteristic symptoms; autopsy showed isolated unilateral hemorrhage in nucleus subthalamicus. (This nucleus does not belong to the basal ganglia sensu strictiori, but it is included because it is closely related to these structures.)

The eight cases of choreo-athetosis (1, 57) were all progressive, and they all had degenerations of nucleus caudatus and putamen; in seven cases lesions were found in globus pallidus, in five in nucleus subthalamicus and only one case had changes in cortex cerebri.

This group of cases differs from our case with regard to the time of onset of symptoms, with regard to hyperkinesia and with regard to the degenerative changes of medulla oblongata and medulla spinalis which are characteristic of our case.

Paralysis agitans (17, 24). A characteristic finding is lesions of substantia nigra. We have gone through five reports (23, 57) from the literature; all showed degenerations of caudatus and putamen, four showed lesions in globus pallidus, three in nucleus subthalamicus, four in cortex, but only one in substantia nigra. With regard to the distribution of the lesions of the basal ganglia this group cannot be distinguished from the group just mentioned (senile chorea) and it differs from our case in the same ways.

Infectious etiology (29) of lesions in the basal ganglia as known in Sydenham's rheumatic chorea can be excluded in our case both from a clinical and pathoanatomical point of view.

Tumours (39) localized to the basal ganglia can produce symptoms of hypertonicity and hyperkinesia but the slow progression, the encephalogrammes and the post-mortem findings exclude this diagnosis.

Several *intoxications* (11, 53, 65) may mainly produce lesions of the basal ganglia; among these the best known is carbon monoxide (symmetrical degeneration of globus pallidus, and very rarely choreiform hyperkinesia). Similar lesions and clinical pictures can be seen after intoxications with cyanide, lead, manganese, phosphorus and also after hypoglycemia and injuries (32).

Torsion spasm (dystonia musculorum deformans) (25, 35, 42, 51, 59) has many resemblances to our case both clinically and pathoanatomically, for which reason we shall discuss some cases reported in the literature. Out of seven patients (12, 13, 36, 63) three were females and four males. Without previous significant illness their symptoms started between the age of 5 to 14 years (in one case the disease may have started following whooping-cough at the age of 6 weeks). The duration of the illness was from 2 to 22 years, most often more than 10 years. The symptoms were progressive. In the literature a familial occurrence is sometimes reported, but the above mentioned were sporadic.

Disturbances of gait with stiffness or weakness of one or both legs were the first symptom in 4 of the 7 cases. Later on involuntary movements developed. Sudden death occured in three cases. The hyperkinesis is described as spontaneously occurring, sometimes constant, slow, writhing move-

ments including the extremities, head and body, leading to torticollis and tortipelvis. Sometimes painful muscle spasms occurred. Clinically our case differs from the above mentioned cases of torsions spasm through the paucity of spontaneous hyperkinesis. Pathoanatomically we find similarities and differences. The similarities consist in lesions of the caudate nuclei, the putamina, globus pallidus, substantia nigra, medulla oblongata, the spinal cord and the cortical grey matter.

The differences consist in the absence in our case of abnormal amounts of iron pigment and lipochrome; in the absence of changes in the dentate nuclei and in the absence of pronounced degeneration of the cortical grey matter. The most striking difference is the severe acute degeneration in medulla oblongata and in the grey matter of the spinal cord in our patient.

Six reports of cases of lesions of the basal ganglia characterized by progressive course and by onset of symptoms at the age of three to ten years (4, 20, 27, 34, 50, 62). From the informations given in the reports it could be concluded in every case that there was a "free interval" of several years from a normal birth until the onset of symptoms. Unfortunately informations regarding neonatal jaundice were not given.

In three of the six cases the condition was familial. Common to these three cases was the finding of microscopical lesions of cortex cerebri and degeneration and excessive amounts of pigment in globus pallidus and in substantia nigra. In two cases both putamen and caudatus were affected. All three children showed mental debility, one had retinitis pigmentosa, one optic atrophy, one had athetosis and two showed rigidity without hyperkinesia.

In all of the three non-familial cases degenerative processes were found in cortex cerebri, nucleus caudatus, putamen, and globus pallidus; they were all mentally retarded, had athetosis and rigidity.

If our case is compared with the two subgroups of the last mentioned six cases the differences will be more obvious than the similarities

Some Remarks on the Relationship between Pathology and Symptoms

In the discussion the various clinical symptoms, especially the motor functions have been related to the pathoanatomical findings, but it seems to be difficult to draw conclusions regarding the importance of the individual nuclei to the various abnormal motor functions (hypertonicity, athetosis, torsion spasm, tremor) (2, 6, 21, 60). For instance, it may be mentioned that both choreo-athetosis and paralysis agitans are associated with lesions of nucleus caudatus + putamen; on the other hand, athetosis in late cases of kernicterus seems to be associated with lesions of globus pallidus while nucleus caudatus and putamen are usually unaffected.

If we examine the symptomatology of isolated lesions of nuclei caudati, putamina and globus pallidus we will only find such lesions in globus pallidus. The clinical symptoms in such cases consist of rigidity with or without hyperkinesia.

It has been claimed that athetosis can only occur if cortex cerebri is unaffected and mature but the correctness of this hypothesis seems to be doubtfull.

Regarding the conclusions which can be drawn from our case it may be stated, that the spasticity and rigidity during the first years of his illness must be ascribed to the older processes of degeneration in nucleus caudatus and putamen. Thus, spasticity and rigidity without spontaneous hyperkinesia, may result from basal ganglia lesions in spite of a practical normal cortex cerebri.

Furthermore an explanation of his sudden attacks of fever and cyanosis and his death in such an attack can be found in the fresh lesions in the reticular substance in medulla oblongata.

Summary

A symmetrical degeneration of the basal ganglia, medulla oblongata and spinal cord, seemingly older rostrally and more fresh caudally, was found in a 10 year old boy who died suddenly after a progressive disease of 8 years duration.

The symptoms consisted in spasticity, rigidity, dysarthria, and abnormal movement patterns resembling torsion spasm. His intelligence was normal. Encephalogrammes showed progressive dilatation of the lateral ventricles, corresponding to the atrophy of the basal ganglia.

The relationship of these clinical and pathoanatomical findings to established clinicopathological syndromes is discussed.

Sur une association de lésions des noyaux de la base, du bulbe et de la moëlle rachidienne chez un garçon de 10 ans.

Un garçon de 10 ans décéda brusquement après une affection progressive qui dura 8 ans. L'autopsie montra une dégénérescence symétrique des noyaux de la base, du bulbe et de la moëlle rachidienne, qui paraissait plus ancienne du côté cranial, et plus récente dans la partie caudale. Le tableau symptomatique était celui d'une association de spasticité, de rigidité, de dysarthrie et de mouvements anormaux analogues à des spasmes de torsion. L'intelligence était parfaitement conservée. L'encéphalographie montrait une dilatation progressive des ventricules latéraux par atrophie des noyaux de la base. La relation entre l'aspect clinique et les lésions anatomopathologiques est ensuite passée en revue.

Kombinierte Erkrankung der Basal-Ganglien, der Medulla oblongata und des Rückenmarkes bei einem zehnjährigen Jungen.

Eine symmetrische Degeneration der Basal-Ganglien, der Medulla oblongata und des Rückenmarkes wurden bei einem zehnjährigen Jungen beobachtet. Die rostralen

Anteile waren dabei offenbar früher befallen als die caudalen Gebiete. Er starb plötzlich nach einem progressiven Leiden von achtjähriger Dauer. Die Symptome bestanden in Spasticität, Rigidität, Lautbildungsstörungen und einem abnormen Bewegungsablauf, der an Torsionsspasmen erinnerte. Seine Intelligenz war normal. Encephalogramme zeigten eine fortschreitende Dilatation der Seitenventrikel entsprechend der Atrophie der Basal-Ganglien. Die Beziehungen zwischen den klinischen und pathologisch-anatomischen Befunden werden diskutiert und die Festlegung eines klinisch-pathologischen Syndroms versucht.

Lesiones combinadas de los ganglios de la base, médula oblongata y médula espinal en un niño de 10 años.

En un niño de 10 años, que murió subitamente a continuación de una enfermedad progresiva de 8 años de duración, se encontró degeneración de los ganglios de la base, bulbo y médula espinal. Dichas lesiones eran mas antiguas en la región craneal y mas frescas en la caudal. La sintomatología, consistente en espasticidad, rigidez, disartria y movimientos anormales semejaba al espasmo de torsión. La inteligencia no estuvo afectada. Diversos EEG mostraron dilatación progresiva de los ventrículos laterales correspondiendo a la atrofia de los ganglios de la base. Se discute la relación entre estos hallazgos clínicos y anátomo patológicos con sindromes clínico patológicos establecidos.

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Inorganic Pyrophosphate in Human Blood?

by CARL-ERIC RÄIHÄ, G. ÅBERG and G. R. WALLGREN

In an earlier paper Räihä (1954) has discussed the possibility that the fraction in human blood which we call "inorganic phosphate" is not uniform, but consists of different phosphate fractions. Benjamin and Hess have absorbed phosphate salts from the blood plasma with different materials such as barium sulfate and ossifying cartilage and observed that about half of the inorganic phosphate will be absorbed, the other half will not. Janda and Göbell have precipitated orthophosphate from blood plasma using Mathison's reagent and noticed that out of the so-called "inorganic phosphate" in blood plasma actually only one third is inorganic phosphate, the rest they presume to be "creatine phosphate". The creatine phosphate fraction has not been further investigated.

As the method published by Flynn, Jones and Lipmann presents a possibility to determine the inorganic ortho- and pyrophosphate from the same solution, we have used this method to investigate the presence of these salts in human blood serum. For comparison, we have simultaneously determined the inorganic phosphate using the "classical" method of Fiske and Subbarow.

Flynn, Jones and Lipmann observed that cysteine added to the mixture of ortho- and pyrophosphate would catalyse the color reaction between eikonogen and pyrophosphate. This reaction will not occur with the Fiske-Subbarow reagent. Cysteine does not have any effect upon the reaction between orthophosphate and eikonogen, which reaction goes to completion 7 min. after the addition of the reagent and can be measured. The pyrophosphate reaction goes to completion *c.* 90 min. after the addition of the reagent.

The following was observed in preliminary experiments with water solutions of pure salts:

1. Seven min. after the addition of reagent, the pyrophosphate did not give any spectrophotometric reading.

2. The reading for orthophosphate increased *c.* 12.0 % in 90 min. This value was used as a correction factor in the investigations of blood.

3. Pyrophosphate could not be clearly shown by use of the Fiske-Subbarow reaction. In three tests performed on samples containing 5 mg % pyrophosphate each, the recovery was only 0.2 mg %.

The blood used in our investigations was handled and stored at low temperature (0° to 4°C) until the color reaction was performed; this occurred at room temperature. It was observed that the orthophosphate reaction decreased 33.1% at low temperature as compared to the reaction at room temperature. The change in temperature had very little effect upon the pyrophosphate reaction.

The analysis was performed by adding 5 ml of 10% trichloracetic acid to 1 ml of plasma for protein precipitation. One ml of the supernatant filtrate was diluted with 7.7 ml H_2O. One ml 2.5% ammonium molybdate, 0.4 ml cystein solution and finally 0.4 ml eikonogen solution were added. The readings were taken with a Beckman spectrophotometer (Model B) at 660 mμ.

By investigating the phosphates of plasma with the above-mentioned methods, it became clear that the fraction generally called "inorganic phosphate" apparently does not exist entirely in the inorganic form. The values using the Fiske-Subbarow method were 1.5 to 2.0 times higher than the corresponding values using the method of Lipmann et al. It seems as though the values for the inorganic phosphate which we get by the use of Lipmann's method are composed of equal amounts of ortho- and pyrophosphate. The orthophosphate values obtained in this way correspond closely with those values which Janda & Göbell obtained by precipitating the salts.

When we investigated the phosphate fractions in different age groups, it was observed that the phosphate fraction decreases as the age increases, when the Fiske-Subbarow method is used. This finding fully corresponds with the current view. The values, when using the method of Lipmann *et al.*, on the other hand, do not decrease with increasing age. The ortho- and pyrophosphate values increase until the first year of life when they start to decrease, reaching a minimum at the age of three years. Later in life they tend to stay unchanged. We observed further that both fractions were usually higher in venous blood than in arterial blood.

Results obtained before and after bodily strain showed that the pyrophosphate fraction decreases in both venous and arterial blood, while the orthophosphate fraction remains unchanged. The phosphate values obtained by the Fiske-Subbarow method increased in the venous blood and stayed unchanged in the arterial blood.

We also investigated a number of spinal fluid and urine samples using the method of Lipmann *et al.* Neither of the fluids gave the pyrophosphate reaction.

Acknowledgement.—We want to extend our thanks to Fil. Kand. J. Harri and to Fil. Kand. J. Puranen for their advice and help with the chemical analyses.

Summary

The authors have investigated the inorganic phosphate in human bloodplasma using the methods of Fiske-Subbarow and of Flynn, Jones & Lipmann. The values obtained with Fiske-Subbarow's method seem to be dependent not only on the inorganic phosphate, but also on easily hydrolysed organic P-compounds. Using the latter method, it is possible to detect both inorganic ortho- and pyrophosphate. The pyrophosphate in blood decreases after muscular work. It was also observed that the content of inorganic phosphate was higher in venous blood than in arterial blood. In urine and in spinal fluid no pyrophosphate was found.

Le pyrophosphate inorganique dans le sang humain.

Les auteurs ont recherché la présence du phosphate inorganique du sang humain par les techniques de Fiske-Subbarow et de Flynn, Jones et Lipmann. Les chiffres obtenus en utilisant la méthode de Fiske-Subbarow, ne semblent pas seulement en relation avec le phosphate inorganique, mais également en rapport avec des liaisons avec du Phosphore organique facilement hydrolysées. En utilisant l'autre méthode, il semble donc possible de mesurer à la fois le pyro- et l'ortho-phosphate inorganique. Le pyrophosphate sanguin diminue après un travail musculaire. On a remarqué, de même, que la valeur du phosphate inorganique du sang veineux était supérieure à celle du sang artériel. On n'a pu mettre en évidence de pyrophosphate ni dans l'urine, ni dans le LCR.

Anorganische Pyrophosphate im menschlichen Blut.

Der Autor hat die anorganischen Phosphate im menschlichen Blut untersucht unter Benutzung der Methoden nach Fiske-Subbarow und Flynn, Jones und Lipmann. Die Werte, die mit der Methode nach Fiske-Subbarow erhalten wurden, sind offenbar nicht nur von dem Gehalt an anorganischen Phosphaten abhängig, sondern auch von der Anwesenheit leicht hydrolysierbarer organischer P-Abkömmlinge. Bei der Benutzung der zweiten Methode ist es möglich, sowohl die anorganischen Ortho- wie Pyrophosphate zu erfassen. Die Pyrophosphate im Blut vermindern sich nach Muskelarbeit. Es wurde beobachtet, dass der Gehalt an anorganischen Phosphaten im venösen Blut höher ist als im arteriellen. Im Urin und Liquor wurden keine Pyrophosphate gefunden.

Pirofosfato inorgánico sanguíneo.

Los autores han investigado el fosfato inorgánico en sangre humana usando los métodos de Fiske-Subbarow y Flynn, Jones y Lipmann. Los valores obtenidos por el método de Fiske-Subbarow parecen depender no solamente del fosfato inorgánico sino también de los compuestos de P inorgánico facilmente hidrolizados. Usando el segundo método es posible detectar tanto el orto como el pirofosfato inorgánicos. El pirofosfato sanguíneo disminuye después del trabajo muscular. Se observó asimismo que el contenido de fosfato inorgánico era mas alto en la sangre venosa que an la arterial. En orina y líquido cefalorraquídeo no se encontró pirofosfato.

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High Protein Nutrition in Prematures by Means of Casein Supplement to Human Milk[1]

by ARNE ROTHE-MEYER and ERIK SANDØE

The well founded opinion that human milk represents the best nutrition also for premature infants recently has been challenged by critics maintaining that the protein and salt content of human milk is insufficient for the requirements of the premature baby. Some authors (Levine & Gordon, Mackay & Levin) have recommended the use of acidified half skimmed cow's milk as a feeding high in protein and poor in fat; other authors have preferred to reinforce human milk with some kind of protein. By an amino acid supplement to human milk Magnusson obtained remarkably increased weight gains, while Hess & Lundeen got similar results by adding acidified skimmed cow's milk to human milk. The discussion on the pros and contras of high protein nutrition is still as much alive as is the discussion on what is the best feeding for premature infants (Ford, Young *et al.*, Crosse).

In previous investigations one of us (Rothe-Meyer) has shown, that between the fourteenth and forty second days of life the daily weight gain in prematures fed on half skimmed citric acid milk was significantly higher than in those fed on human milk. The level of total serum protein and of serum albumin was higher in the infants on citric acid milk than in the infants on human milk, while the level of serum globulin was the same in the two groups. Finally it was shown that citric acid milk produced a higher level of blood urea than human milk, a finding that may imply an increased renal strain in the prematures fed on citric acid milk.

Most pediatricians willing to accept the increased weight gain of high protein feeding as a biologically desirable result—which has not yet been proved—would prefer to achieve this aim by supplementing protein to

[1] Supported by a grant from The King Christian X Foundation.

human milk instead of feeding cow's milk mixtures. As the casein hydrolysates introduced by Magnusson are rather expensive the question arose, whether the same effect could be obtained by means of undigested pure casein.

Weight Gain

Since 1948 such experiments have been performed by us with a Danish product "Seccosan" that is made from acidified skimmed milk and contains 90 per cent pure unsplit casein.[1])

The experiments were started during Rothe-Meyer's appointment to the *Children's Hospital, Martinsvej* (B.p.M.) and have been continued there from 1950 to 1954 thanks to the kind cooperation of the successor, Dr. E. W. Flensborg. From 1950, when Rothe-Meyer was appointed to the *Children's Hospital, Fuglebakken* (B.p.F.) and up to 1954 similar experiments have been carried out also at this hospital. This arrangement has made it impossible to keep experimental conditions completely identical. In the final statistical analysis the material thus obtained therefore could not be treated as a whole but had to be treated as three separate groups (B.p.M. before 1950, B.p.M. 1950–54 and B.p.F. 1950–54). In each of these groups the daily weight gain of prematures fed on human milk has been compared to that of prematures fed on human milk with a supplement of 1.5 per cent of Seccosan. The increase of caloric intake caused by the Seccosan supplement did not exceed 5–10 per cent of the total calories. The human milk was obtained either from the mother or from a human milk bank.

A considerable number of the premature babies were not admitted to the pediatric hospital directly after delivery but only during the first or second week of life. As in the previous experiments we therefore choose the period between the fourteenth and forty second days of life for investigation.

In Table 1 are recorded the prematures the studies of whom did not have to be interrupted because of untimely death, discharge, change of formula or severe complications. Each hospital group has been divided into subgroups according to the type of feeding (human milk solely = − S, human milk with 1.5 per cent Seccosan = + S) and according to the birth weight (below 1500 g, 1500–1990 g, 2000–2500 g).

In all weight groups the *mean values of the daily weight gain* during the

[1] The manufacturer, "Ferrosan", Copenhagen, has kindly supplied the following analysis of "Seccosan":

Protein	ca.	89 %
Lactose	,,	1.5 %
Fat	,,	1.5 %
Ashes	,,	3 %
Water	,,	5 %

100 g powder contains 375 cal. Sodium content is about 0.3 per cent.

TABLE 1

Mean and difference of the daily weight gain in g in prematures fed on human milk (− S) and on human milk with Seccosan supplement (+ S).

B.p.M. = Children's Hospital Martinsvej
B.p.F. = Children's Hospital Fuglebakken

Birth weight		< 1500 g		1500–1990 g		2000–2500 g	
Human milk		− S	+ S	− S	+ S	− S	+ S
B.p.M. before 1954	Weight gain	19.1	32.5	22.6	32.5	27.8	
	Difference	13.4		9.9		—	
	No. of cases	3	8	26	8	13	0
B.p.M. 1950–54	Weight gain	22	29.9	26.2	31.0	24.1	29.9
	Difference	7.9		4.8		5.8	
	No. of cases	2	37	21	115	19	20
B.p.F. 1950–54	Weight gain		22.4	19.8	26.4	20.4	27.4
	Difference			6.6		7.0	
	No. of cases	0	8	17	62	24	19

period from the fourteenth to the forty second day are significantly higher in the prematures fed on human milk with Seccosan supplement than in those fed on human milk solely. The daily weight gain on human milk being about 20–25 g and that on Seccosan supplemented human milk being at least 5–7 g higher, the increase caused by Seccosan (20–30 per cent) cannot be due solely to the increased caloric intake through the supplement.

We are not able to give a satisfying explanation of the pronounced variations of the absolute values in the various groups of Table 1. One interesting finding however should be mentioned. All the figures for daily weight gain of the Fuglebakken Hospital are on a lower level than those of the Martinsvej Hospital, probably because B.p.F. has been more cautious in regard to feeding quantities. Nevertheless the effect of Seccosan is quite as or even more evident here, thus demonstrating that the Seccosan effect is not dependent on the absolute level of weight increase.

Serum Proteins and Blood Urea

Having shown that Seccosan supplement to human milk is able to produce a weight increase of the same order as citric acid milk, the effect of Seccosan on the serum proteins and on the blood urea will now be reported (Table 2). Investigations of this kind have only been done at Martinsvej before 1950 and at Fuglebakken 1950–54. As in the previous work the *serum proteins*

TABLE 2

Mean and variance of total protein, albumin, globulin and blood urea in prematures fed on human milk (− S) and on human milk with Seccosan supplement (+ S).

B.p.M. = Children's Hospital Martinsvej
B.p.F. = Children's Hospital Fuglebakken

Serum protein

	Human milk	No. of cases	Total protein g %	Albumin g %	Globulin g %
B.p.M.	− S	33	4.3	3.2	1.0
before 1950	+ S	6	4.8	3.8	1.0
B.p.F.	+ S	67	4.8	3.6	1.2
Variance			0.254	0.297	0.106
Degrees of freedom			105	102	102

Blood Urea

	Human milk	No. of cases	Urea mg %	Variance of log	Degrees of freedom
B.p.M.	− S	33	8.6	0.02508	32
before 1950	+ S	15	28.9	0.02151	14
B.p.F.	+ S	67	19.5	0.00945	66

were determined by the method of Henriques and Clausen comprising Kjeldahl and using half saturation with ammonium sulfate for the precipitation of globulin. The urea estimations of the B.p.M. group had to be done at a commercial medical laboratory, which used the van Slyke & Cullen method, while the determinations of the B.p.F. group were made at the Fuglebakkens Hospital with the van Slyke & Kugel modification of the van Slyke method. For the statistical analysis only one observation on each infant during the age period 35 to 42 days has been used. Neither the proteins nor the blood urea showed any statistical correlation to the birth weight which has therefore been disregarded.

The results of the biochemical determinations recorded in Table 2 permit the following conclusions in regard to serum protein: The feeding of human milk with Seccosan supplement causes a slight increase of serum *albumin* and consequently of *total protein*, while serum *globulin* does not undergo any significant changes. This conclusion is confirmed by the fact that there is no statistical difference between the two Seccosan groups (B.p.M. before 1950: +S and B.p.F: +S).

The Seccosan supplement also causes an increased level of *blood urea*. The discrepancy between the figures of the two Seccosan groups (B.p.M. before 1950: +S and B.p.F: +S) may have several causes. The above mentioned difference of laboratory methods is not sufficient to explain the discrepancy. In our opinion it is primarily due to the more cautious feeding attitude at the Fuglebakken Hospital. Though a control group for human milk is lacking we venture to state that even the blood urea values of the B.p.F. group on Seccosan supplement represent an increased level still lying within the normal range.

Conclusions

These investigations have shown that a supplement of pure undigested casein to human milk is able to produce a similar increase of the *daily weight gain* in prematures as has been obtained by adding amino acids and skimmed cow's milk to human milk. The casein supplement also produces a rise of serum protein and blood urea analogous to that caused by feeding half skimmed citric acid milk to prematures.

These findings are apt to illustrate the difficulties met with in the discussion of the benefits and disadvantages of high protein feeding to prematures. On the one hand there is complete agreement to the fact that increased daily weight gain *per se* does not necessarily mean more healthy thriving. The rise of the level of serum protein (caused by albumin) does not permit any conclusive interpretation and more convincing evidence in the form of reduced mortality and morbidity is still missing.

On the other hand several authors have cautioned against high protein feeding to prematures. Darrow *et al.* found a tendency towards acidosis and similar results were obtained by Dupont in our early series of prematures fed on half skimmed citric acid milk. Kagan *et al.* deny any benefit from high protein feeding and maintain that the weight increase is simulated by an increased salt and water retention in the body. In conformity with the raised blood urea levels found by us, these observations tend to imply an increased strain upon the organism and thus lead to the question, whether a moderately raised urea level is a sign of increased renal strain. We are not able to give a satisfying answer but want to point out that the blood urea values found by us in prematures fed on high protein diet are of the same order as those found in infants fed on ordinary cow's milk mixtures.

Extract from Statistical Report

The statistical analysis and extract have been made by Arne Nielsen, Lic. Act., statistician to the Danish Cancer Register.

Weight Gain

The daily weight gain during the period from the fourteenth to the forty second day of life has been analysed with regard to the five factors: Hospital, year of birth, nutrition, birth weight and whether tube feeding was used or not. Thirty-six groups are possible with these divisions.

For the groups comprising a sufficient number of infants the distribution of these according to daily weight gain has been drawn on probit paper. The points were grouped around a straight line showing that the assumption of a normal distribution was well founded. The group of infants from Fuglebakken on human milk diet with a supplement of Seccosan, with a birth weight between 2000 and 2500 g, and not being tube fed, constitute an exception since some of these infants have a large daily weight gain. Nevertheless in the computations it has been assumed that the distribution of the infants is normal in all groups.

From a comparison of the estimates of the variance for each group it may be assumed that the variance in groups of infants with the same nutrition is the same. The estimate of variance in groups of infants fed on human milk + Seccosan is significantly higher than the estimate of the variance in groups of infants fed on human milk solely. The variance ratio is $v^2 = 1.48$ ($f_1 = 261$, $f_2 = 106$) (Hald) and this value is significant with respect to the 5 per cent level. If the large estimate in the above mentioned group is omitted the significance will disappear.

In the following comparisons of the means the joint estimate of the variance for all groups has been used and this is equal to 21.64 with 367 degrees of freedom.

The comparisons by *t*-tests of the means of infants from Martinsvej born respectively before and after 1950 show two significant deviations between the means with respect to the 5 per cent level but no regular tendency to higher or lower means for infants born later than 1950 than for those born previous to this year.

The *t*-tests for differences between the means of tube fed infants and infants not fed by tube show no significant deviations and joint means for the groups are therefore computed. In Table 1 are recorded the resulting values and the number of infants in the groups. The table also shows how much higher the daily weight gain is in the infants getting Seccosan supplement to human milk. All these differences are significant with respect to the 0.1 per cent level except one which is significant with respect to the 5 per cent level.

Table 1 also shows that there seems to be no regular correlation between the daily weight gain and the birth weight.

Total Protein, Albumin, Globulin and Blood Urea

In many infants from Fuglebakken determinations of total protein, albumin, globulin and blood urea have been made both at the age of about forty days and at the age of about fifty days. It has been shown that for these infants and for this age-period there is no significant increase or decrease in any of the four determinations.

For the expression of the level of the determinations only one observation of each of the four determinations has been used preferably from the age period thirtyfive to fortytwo days. For each of the groups into which the material has been divided, the distribution according to total protein, albumin, globulin and blood urea has been drawn on probit paper leading to the assumption that the distributions of total protein, albumin and globulin is normal and that of blood urea is log-normal.

The means and variances of the groups have been analysed in the following way.

There are three main groups: Infants from Fuglebakken + Seccosan, infants from Martinsvej born previous to 1950 –Seccosan and infants from Martinsvej born previous to 1950 + Seccosan. In each of these main groups the variances of the subgroups may be assumed to be identical, and this result applies to each of the four estimations. It has furthermore been shown by variance ratio tests that the means of the subgroups may be assumed to be identical, Total estimates for the mean and variance of the three main groups have then been computed and recorded in Table 2.

By means of Bartlett's tests it has been found that the variances may be assumed to be identical in the three main groups for total protein ($\chi^2 = 1.99$, $f = 2$, not significant) and for albumin ($\chi^2 = 5.10$, $f = 2$, not significant). For globulin ($\chi^2 = 6.70$, $f = 2$, significant with respect to the 5 per cent level), despite the significance, it will also be assumed that the variances are identical, but for blood urea ($\chi^2 = 12.0$, $f = 2$, significant with respect to the 1 per cent level) different variances in the three main groups have to be assumed. In Table 2 the values of the variances are recorded together with the degrees of freedom.

Finally by t-tests significant differences have been found with respect to the 5 per cent level for total protein and for albumin between the means of infants from Martinsvej –Seccosan, and of infants from Martinsvej +Seccosan ($t = 2.25$ and $t = 2.31$) but not between the means of infants from Martinsvej +Seccosan and infants from Fuglebakken + Seccosan. Neither of the corresponding differences are significant for globulin. For blood urea the difference between the means of infants from Martinsvej –Seccosan and of infants from Martinsvej + Seccosan and the difference between the mean of infants from Martinsvej + Seccosan and of infants from Fuglebakken + Seccosan is significant with respect to the 0.1 per cent level ($t = 10.6$, when the largest variance is used and $t = \div 4.82$).

Summary

An increase of the *daily weight gain* in prematures was obtained by adding pure undigested casein to human milk (1.5 per cent "Seccosan"), the effect being of the same order as that reported for other kinds of high protein nutrition.

The Seccosan diet produced an increased level of serum *albumin* and consequently of *total protein*, while serum globulin did not undergo any significant changes. The Seccosan diet also produced an increased level of *blood urea*. These biochemical changes correspond to those caused by a diet of half skimmed citric acid (cow's) milk.

An increased daily weight gain does not necessarily constitute evidence of better thriving. As several observations including the rise of blood urea levels might be interpreted as indicating an increased renal strain, it has been emphasized that the urea values are of the same order as those found in full term infants fed on ordinary cow's milk mixtures.

Les effets d'une augmentation de la ration protidique dans l'alimentation du prématuré, au moyen d'une addition de caséïne dans le lait maternel.

L'addition de caséïne pure non digérée au lait maternel (1,5 % de Seccosan) a entrainé une augmentation du gain de poids quotidien chez des prématurés. L'effet obtenu était identique à celui réalisé par d'autres types de régimes hyperprotidiques. Le régime au Seccosan entrainait une élévation du taux de l'albumine sérique, et par suite des protéïnes totales du sérum; à l'opposé, on n'enregistrait pas de modifications

sensibles des globulines sériques. Le régime au Seccosan provoquait en outre une élévation du taux de l'urée sanguine. Ces modifications biochimiques étaient analogues à celles obtenues par l'administration d'un régime comportant du lait de vache demi-écrémé et additionné d'acide citrique. Or, à une augmentation du gain de poids quotidien ne correspond pas nécessairement une amélioration de la croissance. Comme dans plusieurs observations l'élévation de l'urée sanguine pouvait être interprétée comme le résultat d'une augmentation de l'activité rénale, l'auteur met l'accent sur le fait que l'élévation du taux de l'urée est semblable à celle que l'on observe chez des enfants nés à terme, nourris par divers types de lait de vache.

Ernährung der Frühgeborenen mit einer eiweissangereicherten Nahrung durch Zugabe von Casein zur Frauenmilch.

Eine Erhöhung der täglichen Gewichtszunahme bei Frühgeborenen wurde bei Zugabe von reinem unverdautem Casein zur Frauenmilch (1,5 % „Seccosan") beobachtet. Der Effekt lag grössenordnungsmässig etwa in gleicher Höhe wie er auch bei andersartiger Eiweissanreicherung der Nahrung berichtet wurde. Die Seccosandiät verursachte eine Erhöhung des Serum-Albumin-Spiegels und dementsprechend auch eine Erhöhung des Gesamtproteingehaltes. Das Serum-Globulin zeigte keine eindeutigen Veränderungen. Die Seccosandiät verursachte auch einen erhöhten Blutharnstoffspiegel. Diese Veränderungen entsprechen denen, die bei einer Diät mit halbentrahmter Zitronensäure-(Kuh-)Milch auftreten. Eine Erhöhung der täglichen Gewichtszunahme ist nicht gleichbedeutend mit besserem Gedeihen. Obwohl verschiedene Beobachtungen — einschliesslich der Erhöhung des Blutharnstoffspiegels — als ein Hinweis für eine vermehrte renale Belastung gewertet werden könnten, wird ausdrücklich betont, dass die Harnstoffwerte von der gleichen Grössenordnung sind, wie sie bei ausgetragenen Kindern gefunden wurden, die eine gewöhnliche Kuhmilchmischnahrung erhielten.

Alto aporte proteínico, en la alimentación del prematúro, per medio del agregado de caseína a la leche humana.

Agregando caseína pura no digerida a la leche humana (1,5 % de "Seccosan") se obtuvo un aumento en la curva de peso diaria de prematuros, efecto del mismo orden de los obtenidos con otra clase de alimentación de alto contenido proteico. La dieta con "Seccosan" produjo un aumento de la albúmina sérica, y consecutivamente de la proteinemia total, mientras la fracción globulina no mostró ningún cambio significativo. Un nivel aumentado de la urea sanguinea también fué notado. Estos cambios bioquímicos se corresponden a los obtenidos con una alimentación con babeurre. Un aumento de peso diario no implica necesariamente evidencia de mejores condiciones. Como varias observaciones, incluyendo el aumento de la uremia, pueden ser interpretadas como indicando una mayor exigencia renal, se enfatiza el hecho de que los valores de urea son del mismo orden que los hallados en niños a término alimentados con las mezclas corrientes de leche de vaca.

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Pseudo-Hirschsprung'sche Erkrankung bei einem Myxödem-Säugling

von TOIVO SALMI und PIRKKO LAHESMAA

Als Begleitsymptome des Myxödems sind seit jeher intestinale Unstimmigkeiten bekannt. Am häufigsten sehen wir Verstopfung infolge Darmatonie. Ferner ist in Verbindung mit dem Myxödem eine abdominale Distension (Escamilla, Lisser, Shepardson; Dorff, Stoloff; Stepanow) samt funktionellem Mega- und Dolichocolon beobachtet worden; mitunter erscheinen der ganze Darm, vielleicht sogar der Magen dilatiert (Ravault, Plauchin, Guinet). Man hat die durch Hypothyreose bewirkte Atonie und Dilatation des Darmes mit Thyreoidea-Extrakt günstig beeinflussen können. Diese Veränderungen sind also bei rechtzeitigem Eingreifen reversibel.

Beim myxödematösen Neugeborenen oder Säugling, bei dem sich das die Krankheit kennzeichnende Körperbild noch nicht hat ausbilden können, sind die Darmatonie infolge Mangel an Schilddrüsenhormon und mit dadurch bedingter Obstipation, sowie die Auftreibung des Bauches oft das erste Anzeichen der Erkrankung (Palmén). Das klinische Bild ähnelt dabei in irreführender Weise dem der Hirschsprung'schen Krankheit, besonders wenn auch noch röntgenologisch ein Megacolon festgestellt wird.

Wir stellen kurz einen Fall dar, in dem es auf solche Weise zur Fehldiagnose einer Hirschsprung'schen Krankheit kam.

Fall: S. T. Mädchen, geb. am 31.10.1954. Erbanlage: keine Besonderheiten. Geburtsgewicht: 4000 g, Geburtslänge: 51 cm.

Nach 3 Wochen Brusternährung erfolgte Übergang zu Halbmilch. Dabei wurden die bis dahin normalen Faeces hart. Da das Kind 2 Tage ohne Defäkation blieb, wurde es am 26.11.54 in die Kinderklinik der Universität Turku eingeliefert. Die Mutter teilte mit, der Bauch habe von Anfang an ein eigentümlich gedunsenes Aussehen gehabt, so dass diesem Merkmal bei der Untersuchung die Hauptaufmerksamkeit zugewandt wurde. Eine Röntgenaufnahme des Abdomens zeigte reichlich Luft im Darm, aber keine Flüssigkeitsspiegel. Sonstige Besonderheiten wurden bei der Untersuchung nicht festgestellt, der Darm arbeitete normal. Daher wurde die Patientin nach 5 Tagen Krankenhausaufenthalt wieder entlassen. Bereits 9 Tage später, am 9.12., kehrte das Kind wegen einer Gastroenteritis in die Klinik zurück. Neben den üblichen Durchfallsymptomen richtete sich die Aufmerksamkeit wieder auf die

Abb. 1.

Gedunsenheit des Bauches. Die Röntgenaufnahme des Abdomens zeigte abermals einen grossen Luftgehalt des Colons. Nach Beendigung des Durchfalls wurde eine irrigographische Untersuchung vorgenommen, die im Seitenbild deutlich eine Hirschsprung'sche Verengerung an der Grenze vom Sigma zum Rectum erkennen liess (Abb. 1). Bei einer weiteren Röntgenuntersuchung zeigte sich das Lumen des Dick-

Abb. 2.

darms vergrössert. Das Krankheitsbild liess sich als typisches Megacolon congenitum deuten. Wir entschlossen uns zu einer konservativen Therapie.

Schon bei dieser 2. Untersuchung wurden beim Kind leichte myxödematöse Symptome beobachtet. Wir bestellten es daher zu einer Nachuntersuchung. Es kam bereits nach 3 Wochen wegen einer Infektion der Luftwege in die Poliklinik; das Kind war

jetzt genau 3 Monate alt. Nunmehr zeigte es ein typisch myxödematöses Aussehen. Die Glandula thyreoidea war bei der Palpation nicht zu fühlen. Der Darm arbeitete langsam, die Defäkation erfolgte im Abstand von 3–4 Tagen. Auch die Reaktionen und Bewegungen des Kindes waren auffallend träge.

Die Laboratoriumsuntersuchungen brachten keine für Myxödem typischen Werte. Eine Anämie bestand nicht. Das Blut enthielt 8,4 mg % Kalzium und 6,2 mg % Phosphor; die alkalische Phosphatase war auf 2,2 Bod. Einh. herabgesetzt, die Cholesterinmenge betrug 185 mg %. Die Bestimmung des Serumprotein-Jods misslang leider. Das EKG zeigte eine geringe Niederspannung. Bei dem geringen Alter des Kindes konnten deutlich positive Ergebnisse der Laboratoriumsuntersuchungen nicht erwartet werden. Aber auf Grund des ausgeprägten klinischen Bildes leiteten wir eine Thyreoidin-Behandlung ein. Die Menge des Thyreoidins wurde im Abstand von einigen Wochen von 1 × 0,01 über 3 × 0,01 auf 3 × 0,05 erhöht; jetzt erhält das Kind fast schon ein Jahr lang die Erhaltungsdosis von 2 × 0,1. Schon nach einer Behandlungswoche wurde das Kind sichtlich lebhafter und im weiteren Verlauf der Behandlung verlor es allmählich das myxödematöse Aussehen. Nach 3 Wochen Thyreoidin-Verabreichung wurde eine neue irrigographische Untersuchung vorgenommen. Das Ergebnis verblüffte. Der Dickdarm war jetzt gleichmässig mit Kontrastsubstanz ausgefüllt und von der seinerzeit beobachteten langgestreckten Verengerung an der Grenze vom Sigma zum Rectum war nichts mehr zu sehen. Das Lumen des Darmes wirkte an dieser Stelle ganz normal. (Abb. 2.) Der Röntgenarzt meinte, das Colon habe sich bei der vorherigen irrigographischen Untersuchung aus irgendeinem Grunde nicht vollständig mit Kontrastsubstanz gefüllt und daher sei das unvollständig gefüllte Darmstück fälschlich als Hirschsprung'sche Verengerung gedeutet worden.

In der Folgezeit kam das Mädchen regelmässig zur Nachuntersuchung, anfangs in monatlichen, später in zweimonatlichen Abständen. Myxödematöse Symptome haben sich nicht mehr gezeigt. Die Entwicklung verlief ordnungsgemäss (mit 5½ Monaten 6700 g Gewicht u. 62 cm Länge, mit 11½ Monaten 10.170 g und 72 cm). Die Körpergestalt war stets normal, der Bauch richtig geformt; der Darm arbeitete regelmässig. Die Laboratoriumsuntersuchungen brachten normale Werte. Die Ossifikation entsprach dem Alter. Zweimal noch wurde eine irrigographische Untersuchung vorgenommen (im August und im Dezember 1955). Bei jeder Untersuchung füllte sich der Darm vollständig mit Kontrastmittel. Es waren keinerlei Anzeichen einer Hirschsprung'schen Erkrankung oder einer sonstigen Veränderung am Kind mehr zu beobachten. Auch zeigten sich keinerlei Symptome einer Überdosierung des Thyreoidins.

Bei dem oben beschriebenen Krankheitsbild handelte es sich also offensichtlich um ein angeborenes Myxödem, dessen erste Symptome sich am Verdauungstrakt zeigten. Die Verstopfung und der aufgetriebene Bauch wurden zunächst als Hirschsprung'sche Krankheit gedeutet und die Röntgenuntersuchung schien die Diagnose zu bestätigen. Die Normalisierung des Röntgenbefundes bei späteren Untersuchungen erklärte sich folgendermassen:

1. Die Atonie und Dilatation des Darmes konnten durch die Verabreichung von Thyreoidin rückgängig gemacht werden.

2. Die scheinbare Hirschsprung'sche Verengerung der ersten Untersuchung hatte sich, wie oben besprochen, aus einer unvollständigen Füllung des Darmes mit Kontrastmittel ergeben.

Zusammenfassung

Es handelte sich um ein etwa fünf Wochen altes Mädchen mit den zunächst für Hirschsprung'sche Erkrankung typischen Röntgenveränderungen. Langsam entwickelte sich bei ihm das für Myxödem charakteristische Aussehen. Nach einer Thyreoidin-Behandlung verschwand das myxödematöse Erscheinungsbild sowie die intestinalen Veränderungen.

Pseudo-Hirschsprung in a Myxoedematous Infant.

Report of a case of typical roentgenological and clinical Hirschsprung's disease in a female infant aged 5 weeks. Characteristic myxoedematous appearance developed gradually. Thyreoidin treatment produced disappearance of the myxoedema as well as of the intestinal signs and symptoms.

Pseudo-maladie de Hirschsprung chez un nourrisson myxoédémateux.

L'auteur rapporte un cas radiologiquement et cliniquement typique de maladie de Hirschsprung chez une petite fille de cinq semaines. On vit se développer progressivement des signes d'un moxœdème caractéristique. Un traitement par la Thyroïdine amena une disparition progressive de l'hypothyroïdie, ainsi que des signes de l'affection intestinale.

Pseudo Hirschsprung en un lactante mixedematoso.

Se comunica un caso que presentó una imagen radiológica y cuadro clínico típicos de enfermedad de Hirschsprung. El paciente, de 5 semanas de eded, desarrolló gradualmente una apariencia típicamente mixedematosa. El tratamiento con tiroidina produjo la desaparición tanto del mixedema como de los síntomas y signos intestinales.

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From the Pediatric Department, Sundby Hospital, Copenhagen
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Kartagener's Triad
Situs Inversus, Bronchiectasis, and Sinusitis
Report of a Case

by TAGE SAMSØE-JENSEN

The common association of bronchiectasis and sinusitis with visceral transposition was established by Kartagener. (Kartagener 1933 and 1935, Kartagener & Horlacher).

Co-existence of situs inversus and bronchiectasis is far more common than might be expected according to the statistical occurrence of the two anomalies. Necropsy studies and systematic X-ray examinations (Kartagener 1933, Adams & Churchill, Torgersen) have disclosed situs inversus in one out of 8000 persons. In large autopsy materials (Kartagener 1933) bronchiectasis was present in 1.5 per cent.

Adams & Churchill found bronchiectasis and rhinosinusopathy in 21.7 per cent of 23 patients with situs inversus, whereas bronchiectasis occurred in only 0.3 per cent out of a hospital series of more than 230,000 patients. Similarly, Olsen found 14 (16.5 per cent) to have bronchiectasis in 85 patients with situs inversus, while bronchiectasis had been found in less than 0.5 per cent of all patients admitted to the Mayo Clinic from 1920 to 1941. Torgersen reported this triad of symptoms in 14 out of 129 with visceral transposition. He states that about 10 per cent of all persons with situs inversus suffer from bronchiectasis and nasal disorders.

According to Taiana, Villegas & Schieppati a total of about 100 cases of this syndrome, called the Kartagener triad, have been reported.

Recently, a patient was admitted to our Department:

Case Report

B. J., boy aged 7 (rec. No. 547/1955). No. 2 of a family of 5. The other 4, 2 of whom are identical twins, are in good health. The family history is negative. The boy's parents are first cousins. Delivery was uneventful, and the birth weight 3500 g. Ever since the first postnatal day he has exhibited pronounced râles in the chest and suffered from attacks of coughing and febrile bronchitis. He has always "had a cold" with purulent discharge and nasal stenosis. At the age of 2 years dextroposition of the heart was diagnosed. At 4 and 6 years of age the patient had adenotomy. In March–May 1955 he was admitted to an otologic department. Treatment with antral

aspiration and irrigation, antral resection by the method of Claoué, and a third adenotomy proved ineffective in dealing with the purulent sinusitis. No nasal polyps were present. On May 31, the boy was transferred to the Pediatric Department with bronchitis.

Physical examination showed a boy of normal build and nutrition. Height 128.5 cm, weight 26,100 g. There was slight dyspnoea with audible râles and wheezing. Clearly, the upper air passages were obstructed. Auscultation revealed normal heart sounds in the right side of the chest. Over all lung fields sibilant rhonchi; moist râles basally in both posterior fields. No clubbing of the fingers or curved nails.

X-ray findings: Complete transposition of viscera.

ECG: Genuine dextrocardia. Blood study: Haemoglobin 92–100 per cent.

W.B.C. 10,700—with a normal distribution on differential count.

E.S.R. normal (6–9–6 mm/h). Urinalysis normal. Tuberculin skin test positive (following BCG vaccination).

Since the prolonged clinical course aroused a suspicion of bronchiectasis, the following chest radiographies were performed:

(1) Tomography: Intensified pattern in lower portions of both lower lobes and streaked densities as in peribronchial infiltration. The bronchi of the left hilum were also surrounded by densities.

(2) Bronchography carried out under general anaesthesia, first on the left: All bronchial branches fill satisfactorily. The bifurcation was clearly visualized and proved to be normal. In the medial part of the lower lobe cylindrical bronchiectasis was found. Some time later the right side was examined: Filling of entire bronchial system. The branches to the lower lobe were dilated and gave rise to a suspicion of cylindrical bronchiectasis in the right lower lobe.

During the stay in the Pediatric Department, until Sept. 25, the temperature was often elevated for long periods, and large doses of water-soluble penicillin were of merely transitory effect.

It was contemplated to refer the boy to continued control in a department of thoracic surgery, but his parents definitely refused. Then, respiratory exercises and training in expectoration were instituted, apparently with a good effect, because of follow-up 3 months after discharge he had not had fever. His sinusitis was unchanged, and otorhinological treatment had been given up.

Discussion

There is some question about the existence of congenital bronchiectasis. Kartagener (1935) himself was a supporter of the theory of the congenital origin of bronchiectasis, as opposed to the prevailing opinion of especially american authors, that it is acquired.

The frequent occurrence of bronchiectasis in visceral transposition, which is a congenital condition, the finding of Kartagener's triad in siblings (Bergstrom *et al.*, Dickey, López Areal and others), and the high incidence (25 per cent) of bronchiectasis in siblings of patients with Kartagener's syndrome (Torgersen) have, however, led to a recognition of the view that in Kartagener's syndrome a genetic factor or a pulmonary maldevelopment may predispose to the bronchial lesions.

From Denmark Blixenkrone-Møller has reported a case in a 3-year-old oligophrenic girl whose pulmonary lesion was cured by lobectomy. He interprets the bronchiectasis in his case as being congenital, and advances arguments which have not been mentioned by others: (1) The histological examination of the removed lobe revealed a very tall columnar epithelium, even in the smallest bronchial branches. This does not indicate secondary dilatation, but rather a congenital condition. (2) The bronchial walls contained an enormous accumulation of lymphoid tissue, regular primary follicles. Such structures are not present in normal bronchi, but they are characteristic of certain congenital abnormalities (e.g. cervical cysts). (3) In addition the symptoms were present from birth.

However, a satisfactory explanation of this triad association has not yet been made. In Adams & Churchill's opinion some cases of situs inversus are normal mutants, whereas others—being true monsters—presumably present the visceral transposition as one link in a congenital malformation, at times co-existing with other congenital malformations such as bronchiectasis.

In our patient the symptoms had been present from birth, and this might indicate that his bronchiectasis was congenital. The pronounced bronchiectatic and prebronchiectatic changes found in his lungs will probably progress and sooner or later necessitate thoracic surgery.

Future genetical investigations and histological studies of resected lung tissue may possibly contribute to the understanding of the aetiology and pathogenesis of the bronchiectasis in Kartagener's triad.

Summary

Kartagener's triad is reported in a 7-year-old boy who had presented bronchial symptoms from birth. The author briefly discusses the frequency of bronchiectasis in situs inversus as well as the views advanced regarding the aetiology and pathogenesis.

Le syndrome de Kartagener (situs inversus, bronchiectasie et sinusite). — A propos d'un cas.

La triade de Kartagener chez un garçon de 7 ans, présentant des signes de l'affection bronchique depuis la naissance, est décrite. L'auteur discute rapidement la fréquence des bronchiectasies au cours du situs inversus, et passe en revue les théories avancées au sujet de l'étiologie et de la pathogénie.

Kartagener'sche Triade: Situs inversus, Bronchiektasie und Sinusitis. Bericht eines Falles.

Bericht eines Falles von Kartagener'scher Triade bei einem 7 Jahre alten Jungen, der seit Geburt bronchiale Symptome zeigte. Der Autor bespricht kurz die Häufigkeit von Bronchiektasie bei Situs inversus sowie die über Ätiologie und Pathogenese vorliegenden Ansichten.

Un caso de tríada de Kartagener: situs inversus, bronquiectasias y sinusitis.

Se comunica un caso de tríada de Kartagener en un niño de 7 años que presentaba síntomas bronquiales desde el nacimiento. La frecuencia de bronquiectasias en relación con situs inversus y las diversas opiniones sobre etiología y patogenia son brevemente discutidas.

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From the Pediatric Clinic, University of Lund, Sweden

Spinal Cord Tumors in Children

by STURE SIWE

To judge from the literature, spinal cord tumors appear to be very rare in children. Stookey found only eight cases under the age of twelve among 460 cases of all ages, Elsberg noted only five under ten years of age among 275 cases, and Hamby collected only 214 cases from the medical literature. Ford had none under five years among his cases.

Since we have had no less than three cases on our service in Lund during a period of ten years, and since none of these patients escaped repeated misdiagnoses before they came to the Children's Hospital, it might be of interest to discuss here briefly the symptomatology. It is self-evident that the diagnosis is not easy, especially in the beginning and for those who are not used to examine children.

Case 1 was two years old and had had symptoms of pains and pareses for eight months before he came to the Pediatric Clinic where he was diagnosed. Due to a severe paralytic ileus which occurred during the earlier part of his hospital stay, his condition was so poor that no operation could be undertaken. At necropsy a ganglioneuroma was found which penetrated from the psoas muscle into the spinal canal and compressed the medulla at the level of L2.

Case 2 was a $2\frac{1}{4}$-year-old girl who had had abdominal pains since six months. She underwent appendectomy in the surgical department, then developed pareses in the legs and was admitted two weeks later to the Children's Hospital where the tumor was diagnosed. She was operated, and an ependymoblastoma in the conus was removed. Three years later she died with pyuria.

Case 3 became ill at the age of nine years, was treated for poliomyelitis and was partially rehabilitated so that she was able to walk again after ten months, but she continued having incontinence of urine and feces. After three years she was operated for appendicitis (healthy appendix), then developed new pareses which improved again. One year later there was an exacerbation of the pareses. She came to the Pediatric Clinic in emaciated condition after having been bedridden for more than a year because of paralysis of the lower trunk and the lower extremities. Incontinence continued. The diagnosis was made, the patient was operated and was found to have an astrocytoma extending from T8 to L3. It was impossible to remove this completely. She improved and died only four years later.

A review of the patients' histories shows that the earliest and, at the same time, the most prominent symptom in all cases was *pain*. This was not al-

ways constant but rather intermittent in character and very severe, especially in the sitting position and, generally, whenever the back was bent and with urination. Obstipation was also a constant symptom as well as difficulty of emptying the bladder. It is worth pointing out that these symptoms occurred, in our cases, equally early whether the tumor was extra- or intramedullary.

The second constant symptom was the *paresis* in the legs (in Case 3 gradually even in the dorsal and abdominal musculature), usually beginning on one side with rather rapid involvement of the other side. The paresis was, strangely enough, not most marked peripherally but spread in a centrifugal direction. In Case 2, there was improvement after operation, in Case 3 remissions for a whole year with renewed exacerbations.

The third constant symptom was *incontinence* which persisted even after operation (Case 2) and during remissions (Case 3). The incontinence affected the bladder as well as, though less markedly, the bowel.

Lumbar puncture revealed either no or, at most, 17 cells per mm^3. The protein content was constantly raised (Bisgaard 1 to 40 till 1 to 1000). In our cases no spontaneous coagulation of the cerebro-spinal fluid and no xanthochromia were present until four years after the onset of symptoms in Case 3.

Sensation was always demonstrably reduced, but the upper and lower limits of these changes were unclear.

Diagnosis of the localization was therefore made with the aid of X-ray myelography.

Some features should be emphasized here which are rarely stressed in textbooks and which can be of help, expecially concerning cases in children:

1. The pain is severe; it increases when the child is forced to try to sit up while the legs are extended. It moves often to the abdomen; this led to operation for suspected appendicitis in two of the three cases. At the onset, the pain is intermittent.

2. Even extramedullary, extradural tumors can early give rise to difficulties with urination and to obstipation, later to incontinence.

3. X-ray of the spine helps with the diagnosis only late in the course of the illness. Myelography is necessary for localization.

4. The high protein content in the CSF is the most constant aspect of Froin's syndrome, while the xanthochromia appears less prominently and later.

5. The pareses have a peculiar character with a mixture of spasticity and flaccidity.

6. Sensory disturbances, which can give much help in adults in the diagnosis and localization, can even aid the diagnosis in small children.

7. Contrary to general opinion, the course is not always evenly or intermittently progressive. We have cases (e.g. Case 3) who show a marked spontaneous improvement of the pareses in the legs for a period of years. Corresponding improvement of the bladder and bowel paresis was not observed in our cases.

Summary

The symptoms of spinal cord tumors in childhood are discussed in connection with three briefly described cases.

Les tumeurs médullaires chez l'enfant.

Discussion des signes des tumeurs médullaires chez l'enfant basée sur l'observation de 3 cas chez des enfants de 2, 2¼, et 9 ans.

Rückenmarkstumoren bei Kindern.

Die Symptome von Rückenmarkstumoren im Kindesalter werden in Verbindung mit dem Bericht von 3 Fällen bei Kindern im Alter von 2, 2¼ und 9 Jahren besprochen.

Tumores medulares en niños.

Se discute la sintomatología de los tumores medulares en la infancia comunicando 3 casos de 2, 2¼ y 9 años de edad.

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From the Pediatric Department (Head: Professor LEIF SALOMONSEN M.D.) and the Neurological Department (Head: Professor SIGVALD REFSUM, M.D.), Rikshospitalet, Oslo

The Significance of Electro-encephalographic Spike Foci in Patients with Cerebral Palsy without Epileptic Seizures

by MARIT SKATVEDT and ARNE LUNDERVOLD

In routine electro-encephalographic examination of children with organic brain disorders, EEG will in some cases show spike foci, even when the patient has had no clinical epileptic fit. The significance of these spike foci is uncertain.

Perlstein, Gibbs & Gibbs state that spike seizures are the most frequent abnormality in their series of EEG in cerebral palsy (1217 patients). Spike discharges were shown in 77 per cent of all abnormal EEG. They found in 44 per cent of the abnormal EEG seizure discharges without clinical seizures. They declare: "The degree of probability that clinical seizures will develop when EEG seizure discharges are present at a given age cannot be stated at present".

Winfield, Hughes & Sayle arrive at the same conclusion. They report "seizure discharges without a history of clinical seizures" in 10 of 128 patients with cerebral palsy of spastic type examined. Further: "Neither the present study nor the ones referred to earlier (Perlstein, Gibbs, and Gibbs) can settle the problem as to whether patients with seizure discharges in the absence of clinical seizures will later develop seizures." At the Pediatric Department, Rikshospitalet, EEG has since 1950 been made in a total of 236 patients with cerebral palsy. All EEG have been registered and described at the EEG Laboratory of the Neurologic Department.

Thirty-four of the patients (14 per cent) showed seizure discharges without having had clinical epileptic seizures. In none of these the spike foci have later disappeared. However, the observation periods have been short.

In three patients epileptic seizures have occurred after the registration of spike foci in their EEG. These cases will be more closely described below.

Patient No. 1.—B. G., girl, born June 5, 1952. History: Erythroblastosis fetalis due to Rh incompatibility between mother and child, treated with exchange transfusion on the first day of life. No clinical symptoms of kernicterus. At the age of 6 months right-sided hemiparesis was diagnosed and she was treated with physiotherapy with

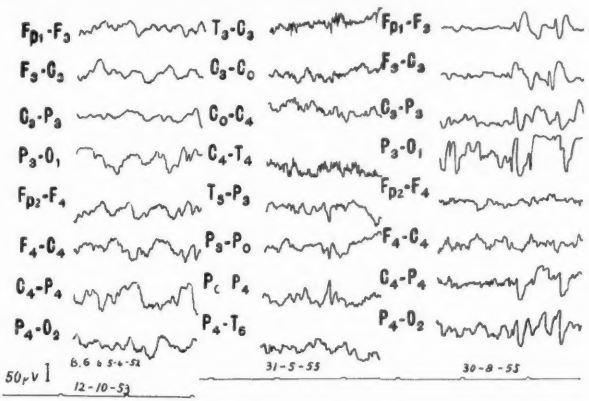

Fig. 1. EEG October 12, 1953, 16 months old, showed a marked focal reduction of voltage in the left central region. EEG May 31, 1955, 3 years old: Sharp waves and focal reduction of voltage in the left central region. EEG August 30, 1955: Spikes in the left central temporal and frontal region.

good result. EEG October 12, 1953, at the age of 16 months, showed a marked focal reduction of voltage in the left central region. EEG May 31, 1955, 3 years old: Sharp waves and focal reduction of voltage in the left central region.

July 8, 1955 she had her first convulsive seizure that lasted for several hours. There were general convulsions with loss of consciousness. She was treated with phenobarbital 0.05, and since then has had no seizure. EEG August 30, 1955; Spikes in the left central temporal and frontal region.

In this case the epileptogenic focus had been registered in EEG five weeks before the first clinical seizure occurred.

Patient No. 2.—R. M., boy, born March 6, 1951. The patient is a twin, the other twin was stillborn. Birth weight 3500 g. The mother had been suffering from anemia during pregnancy, with HGB down to 50 per cent, and in the 7th month of pregnancy she had been given a blood transfusion. The patient has spastic hemiparesis on the right side.

EEG May 11, 1953 (Oslo Municipal Hospital), when well over 2 years old, showed spikes and slow waves in the left frontal region.

Mid-October 1955, when 4½ year old, he had a seizure with general convulsions that lasted for about ½ hour and was followed by sleep. EEG November 30, 1955: Bilateral spikes with maximum in the occipital region.

In this patient the spike focus had been registered 2½ years before the occurrence of the first clinical seizure.

Patient No. 3.—J. W. B., boy, born May 18, 1951. He had been delivered by cesarean section. Birth weight 2700 g. He has a left-sided hemiparesis. EEG November 11, 1954, 3½ years old, showed maximum of slow waves in the right parietal region. EEG November 21, 1955, 4½ year old: Spikes and slow waves in the right parietal region.

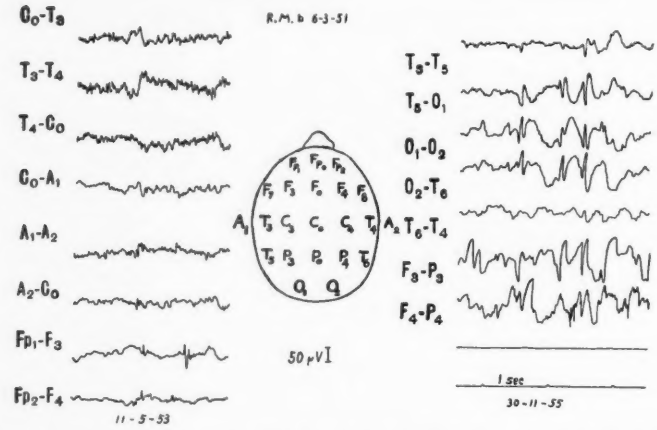

Fig. 2. EEG May 11, 1953, 2 years old, showed spikes and slow waves in the left frontal region. EEG November 30, 1955: Bilateral spikes with maximum in the occipital region.

December 7, 1955 he was admitted to a country hospital in an epileptic seizure. In this case the clinical seizure occurred well over 2 weeks after the registration of spike foci.

In these 3 patients spike foci were registered at the age of 3, 2, and 4½ years, while EEG for patient No. 1, when 16 months old, and No. 3, when 3½ years old, showed no spike foci. Patient No. 2 showed spike foci in the first of his EEG registrations.

The observation period for the 34 patients with spike foci in EEG without clinical seizures is short, and larger series that show the development of the spike foci are not yet available. But the patients will remain under observation. The three reported cases nevertheless suggest that the presence of spike foci in EEG implies an actual danger of the occurrence of manifest epileptic seizures. In the second of the reported cases, 2½ years elapsed from registration of spike focus in the patient's EEG before clinical seizure appeared. In the course of that period he had several illnesses with high fever without a seizure, and at the time of the seizure he had a slight pharyngitis with normal temperature.

Conclusion

The significance of spike foci in EEG in patients who have had no clinical epileptic seizures has been considered as questionable. Three cases are reported in which EEG showed spike foci 2 weeks, 5 weeks and 2½ years before the occurrence of the first clinical epileptic seizure. In two of them the EEG after the seizure showed a considerable increase of the epileptogenic activity.

The observations strongly indicate that spike foci shown in EEG represent an actual danger of later clinical epileptic seizures, but that, as in one of the cases, a long time may pass before the occurrence of the seizure. These patients should be under constant observation. The question of whether or not these patients should be given antiepileptic treatment immediatley after the registration of spike foci cannot be answered at present.

Summary

The significance of spike foci in EEG in patients who have had no clinical epileptic seizures has been considered as questionable. Three cases are reported in which EEG showed spike foci 2 weeks, 5 weeks and 2½ years before the occurrence of the first clinical epileptic seizure. These observations indicate that spike foci shown in EEG represent an actual danger of later clinical epileptic seizures.

Signification des foyers de pointes à l'électroencéphalogramme chez des malades atteints de paralysies cérébrales sans crises d'épilepsie.

Discussion sur la valeur des foyers de pointes à l'EEG de malades atteints de paralysies cérébrales sans crises d'épilepsie. Trois cas sont rapportés dans lesquels l'EEG avait montré l'existence de foyers de pointes 2 semaines, 5 semaines, et 2½ ans avant l'apparition de la première crise convulsive. Ces observations indiquent que les foyers de pointes enregistrés à l'EEG représentent un danger certain de crises convulsives futures.

Die Bedeutung von elektroencephalographischen Spitzenpotentialherden bei Patienten mit cerebraler Paralyse ohne epileptische Krämpfe.

Die Bedeutung von Spitzenpotentialherden im EEG bei Patienten, die keine klinischen epileptischen Krämpfe gehabt haben, sind bisher als fraglich betrachtet worden. Es wird von drei Fällen berichtet, bei denen das EEG 2 Wochen, 5 Wochen und 2½ Jahre vor dem Auftreten der ersten klinischen epileptischen Krämpfe Spitzenpotentialherde zeigte. Diese Beobachtungen weisen darauf hin, dass Spitzenpotentialherde im EEG eine akute Gefahr für spätere klinische epileptische Krämpfe darstellen.

Significación de un foco de "spikes" en los EEG de pacientes afectos de parálisis cerebral sin convulsiones.

La significación de focos de "spikes" en los EEG de pacientes que no han presentado convulsiones se ha considerado como dudosa. Se comunican tres casos en los cuales el EEG mostró dichos focos 2 semanas, 5 meses y 2½ años antes del ataque convulsivo. Estas observaciones indican que un foco de esa naturaleza representa el peligro de futuras convulsiones.

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Baby Pig Mortality and Infantile Pyloric Stenosis[1]

by O. STEINICKE NIELSEN

Despite persistent endeavours, it has not yet been possible to clarify the aetiology and pathogenesis of infantile pyloric stenosis. Within recent years the so-called "neurogenous theory" has received particular attention, because an irreversible degeneration of the intramuscular ganglion cells (Auerbach's plexus) has been found in the pyloric portion of individuals with congenital pyloric stenosis (Herbst, Raia, Alarotu & Christensen, Belding & Kernohan, Steinicke Nielsen). However, we do not know exactly whether this ganglion cell degeneration may be regarded as the primary cause of cong. pyl. sten.

To my knowledge, there has never been found in animals a lesion clinically or pathologically analogous to infantile pyloric stenosis. However, from veterinary medicine we know a complex of symptoms designated as "baby pig disease". These animals are apparently healthy at birth and suck normally. But on the second day of life they become apathetic, weak and disinclined to suck, and the hair coat becomes rough. The pigs often suffer from shivering and vomiting, become dehydrated, and die on the second or third day of life. The aetiology of the condition is obscure. Most likely several diseases are involved. Some workers having found signs of gastroenteritis have attributed the mortality to an infectious disease (Young & Underdahl). Others have demonstrated hypoglycaemia in these newborn pigs (Morrill) and regard this as the cause of the early death. Others again seek the cause in toxic influences from the breast milk (Heidebrecht *et al.*).

The anatomical structure of the stomach and the function of the alimentary canal of pigs resemble those of the human stomach and alimentary canal. Certain features in the clinical picture described above in pigs suggest that a gastric lesion is responsible. I have therefore carried out neurohistological examinations of the intramuscular ganglion cells in the pyloric portion of baby pigs dead with the stated symptoms.

Material and Post-mortem Findings

Stomachs were examined from 26 pigs dead 0 to 2½ days old. These 26 pigs were divided in three groups.

I. Ten pigs with signs of "baby pig disease". All the animals were apparently healthy the first day of life, especially they sucked normally; but on the second day

[1] The work was supported by a grant from P. Carl Petersens Fond.

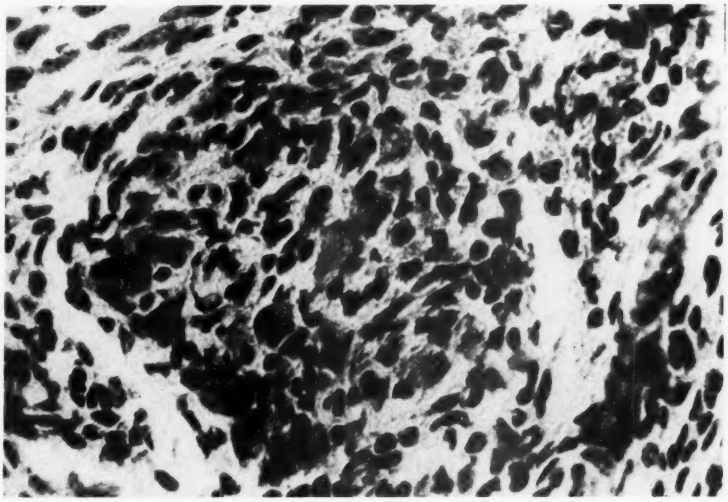

Fig. 1 (Exp. No. 232). Degenerative changes of ganglion from pyloric myenteric plexus (Auerbach) in a pig suffering from "baby pig disease", killed on the second day of life. Ganglion cells chromatolytic and swollen or atrophic and pyknotic. Excessive glial proliferation. Gallocyanine staning, × 500.

they became apathetic and weak; they refused to suck, and 4 of them vomited. Five of the pigs were killed in moribund condition, while the 5 others were found dead.

II. Nine pigs found dead and regarded by the farmers as "overlain" by their respective dams, as none of them had displayed any signs of illness.

III. Seven perfectly normal pigs killed in order to be used as controls.

Only the gastro-intestinal tracts of the pigs were submitted to postmortem examination. In 9 out of the 10 pigs of Group I the stomach was moderately or almost completely full, while one stomach was empty. The intestines of all 10 pigs were practically empty, but with excessive gas contents in the anterior portion of the small intestine.

The 9 pigs of Group II showed the same picture of filled stomach and empty intestines.

In the 7 control pigs both the stomach and the intestines were moderately full.

Further, it may be mentioned that none of the animals presented atresia or other form of mechanical intestinal obstruction. Neither were there found inflammatory changes in the gastrointestinal tract.

The pyloric muscles of the pigs of Groups I and II seemed to be thicker and to extend further proximally than in the controls. However, the material here presented is too small to allow of conclusions regarding the constancy and possible aetiological importance of this finding.

Histological Analyses

All the stomachs were formalin-fixed immediately or few hours after death. Several sections were examined from the duodenum, the pylorus

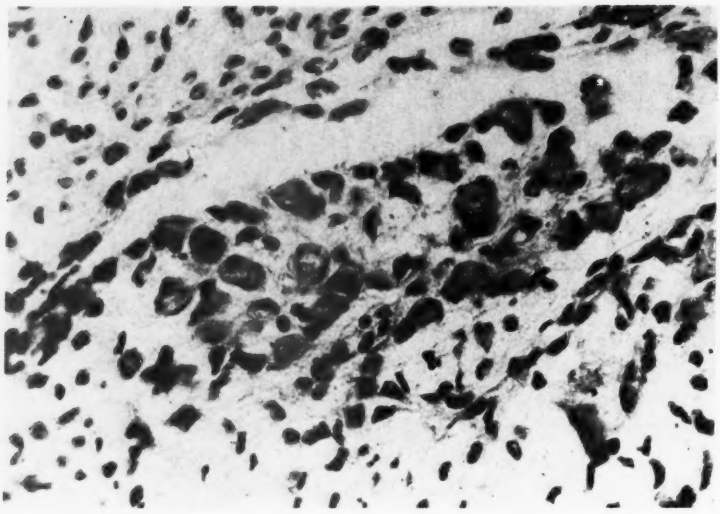

Fig. 2 (Exp. No. 174). Normal ganglion from pyloric myenteric plexus (Auerbach) of a pig killed 3 hours old. Ganglion cells normal or slightly chromophobic (slight cadaverous changes). Gallocyanine staining, × 500.

and the corpus of each stomach. The preparations were stained with haematoxylin–eosin, van Gieson's connective tissue stain and Einarson's gallocyanine stain (Einarson). For the histological analyses I received expert assistance from the neuropathologist Erna Christensen, M.D., whom I wish to thank.

In the cases of all 10 "sick" pigs (Group I) the preparations of the pyloric portion displayed very pronounced degeneration of the intramuscular ganglion cells, manifesting itself party by excessive chromatolytic changes with loss of Nissl's bodies and dissolution of the cells, and partly by atrophic degeneration of the cells. In addition, the ganglia presented marked proliferation of glial tissues. In other words, there were found grave, chronic, irreversible changes (Fig. 1). The duodenal and corporal portions of the same stomachs showed similar changes, but in a less pronounced degree.

Exactly the same picture of irreversible ganglion cell degeneration was seen in the 9 "overlain" pigs (Group II).

In the 7 "healthy" pigs (Group III), on the other hand, the intramuscular ganglion cells were seen to be normal or with slight cadaverous changes in the form of pale and oedematous cells. Atrophic cells or glial proliferation could be seen in none of the cases (Fig. 2).

Conclusion

The histological analyses described above of the intramuscular ganglion cells in the stomachs of baby pigs dead in the stated diseased condition revealed a pronounced irreversible degeneration in the pyloric portion. Identical degenerative changes were seen in the stomachs of the 9 pigs found dead with no recognised disease, whereas no such degeneration was demonstrable in the controls.

There is reason to suppose, on the basis of the macroscopical and the microscopical observations, that the animals of Group II had suffered from the same affection as those of Group I, but that the disease had not been recognised while the pigs were alive, these having therefore been regarded as "overlain".

The degeneration seen in the pigs is analogous to the ganglion cell degeneration found in young infants with congenital pyloric stenosis. The two conditons have other points of resemblance besides the neurohistological picture. First of all they both occur in babyhood. Next there seems to be a familial predisposition both to the disease affecting humans and to that affecting pigs. Thus, the investigations carried out so far on pigs suggest that the progeny of certain sows in certain "families" are particularly liable to become affected. This means that one or two baby pigs in several farrows of the same sow will die of the stated affection.

The present investigations do not allow us to decide whether the condition observed in baby pigs is analogous to infantile pyloric stenosis. If so, this may open out prospects for future studies on the aetiology and pathogenesis of cong. pyl. sten.

Summary

In 10 pigs with clinical signs of "baby pig disease" and in 9 baby pigs found dead without previously recognized signs of disease there was found irreversible ganglion cell degeneration in the pyloric part of the stomach, identical with that found in infants with congenital pyloric stenosis.

Mortalité des porcelets et sténose du pylore chez l'enfant.

L'examen anatomo-pathologique de l'estomac de 10 porcs présentant les signes cliniques de la « maladie des porcelets », et de 9 porcelets morts sans le diagnostic de l'affection ait été porté, révélait l'existence d'une dégénérescence cellulaire dans la région pylorique. Cet aspect est identique à celui que l'on trouve chez les nourrissons porteurs de sténose pylorique congénitale.

Ferkel-Mortalität und infantile Pylorusstenose.

Bei 10 Schweinen mit klinischen Zeichen von „Baby pig disease" und bei 9 Ferkeln, die ohne vorher beachtete Krankheitserscheinungen tot aufgefunden waren, wurde irreversible Ganglienzelldegeneration im Pylorusabschnitt des Magens gefunden, was mit den Befunden bei Säuglingen mit congenitaler Pylorusstenose übereinstimmt.

Mortalidad de cocchinillos y estenosis pilórica.

En 10 lechones con signos clínicos de "baby pig disease" y en 9 encontrados muertos sin que previamente se hubiesen reconocido signos de la enfermedad, se encontró una degeneración ganglionar irreversible en la zona del píloro, idéntica a la encontrada en lactantes con estenosis pilórica congénita.

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From Barnsjukhuset Samariten, Stockholm, Sweden (Head: Prof. NILS MALMBERG)

Atypical Pneumonia in an Infant, Associated with APC Virus Infection

by GÖRAN STERNER

Since 1953 Rowe, Huebner *et al.*, in a series of publications, have dealt with a new group of viruses, the adenoidal-pharyngeal-conjunctival (APC) viruses, which may produce rhinitis, pharyngitis, conjunctivitis and fever in both children and adults. APC virus shares the complement-fixing (CF) antigen with viruses of the RI-67 groups, isolated by Hilleman & Werner from cases of undifferentiated acute respiratory disease. RI-67 viruses, according to Hilleman & Werner, could probably also be responsible for a large portion of the cases of cold-agglutinin negative, primary atypical pneumonia (P.A.P.) among U.S. Army populations. RI-67 also share the CF antigen with the unidentified, possibly new group of cytopathic agents, presumably viral in nature, isolated in 1953 by Kjellén in Stockholm from patients with pharyngitis, tonsillitis and cervical lymphadenitis, and from patients with mesenteric lymphadenitis. In view of the great interest in APC virus at present, it seems justifiable to present here a brief report on a case of atypical pneumonia in an 8-month old girl, in whom we had the opportunity to observe the whole course of the disease.[1]

Case Report

Record No. 1017/55, K. E. A girl born Jan. 15, 1955. Delivery normal; weight at birth 3960 g. Social conditions were very bad, and were the main reason for two earlier hospitalizations with mild acute nasopharyngitis and acute bronchitis in May 1955 and from Sept. 1 to Sept. 10, 1955. During her stay in the hospital in May 1955, a complement-fixation test against APC virus was done with a negative result. At discharge on Sept. 10, 1955, she had completely recovered, except for a persistent very slight cough. On the day after her return home this cough was said to have increased, though there was no simultaneous rise in temperature. She was readmitted on Sept. 14, 1955, this time, too, chiefly on social grounds. Examination on admission showed an afebrile child, weighing 7.1 kg, whose general condition was quite unaffected. Neurological examination showed no abnormalities. There was no dyspnoea

[1] The virological studies in this work were carried out by Dr. Lars Kjellén at the Virus Department of the Central Municipal Bacteriological Laboratory, Stockholm, Sweden (Head: Arne Svedmyr, M.D.). I am deeply indebted to Dr. Kjellén for his kind cooperation.

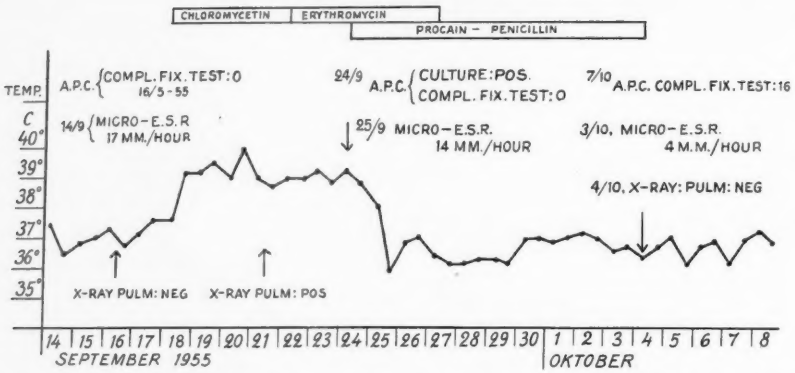

Fig. 1. Temperature chart in the reported case of atypical pneumonia associated with an APC virus infection.

and no cyanosis. Pharynx and tonsils were slightly reddened. Nothing abnormal was detected in superficial lymph nodes, ears, lungs, heart or abdomen. Secretion from nasopharynx yielded no growth on routine culture, nor in two cultures watched especially for any growth of *B. pertussis*. Hb 11.4 g. White cells 6200 (1400 polynuclears). Micro-E.S.R. 17 mm in 1 hour. The urine was normal. *Chest radiogram on Sept. 16, 1955, showed no abnormalities.* Up to Sept. 18 she was afebrile and had a slight cough for which she was given expectorants only.

On Sept. 18, 1955, the temperature rose from 37.6°C in the morning to 39.9°C in the afternoon. On the same day a second sample from the nasopharynx yielded a very scanty growth of *Staphylococcus aureus* and no growth of other organisms. Up to and including Sept. 19, the child's general condition was quite unaffected despite the temperature rise, and examination showed only slight redness of the pharynx. Physical examination of lungs showed no abnormalities. E.S.R. was low. A slow and moderate increase of white cells occurred up to a maximum count of 14,600. The urine was quite normal. Culture of faeces showed a normal bacterial flora. Cerebrospinal fluid was normal. ECG showed no abnormalities. Chloromycetin palmitate suspension (about 80 mg of chloromycetin per kg of body weight and day) had been started on Sept. 18, but in spite of this the condition suddenly changed for the worse on Sept. 20, with dyspnoea and cyanosis, and oxygen was given continuously. Treatment was now changed to intramuscular chloromycetin only, 500 mg twice a day. During the next few days, when her condition was extremely critical, dullness on percussion and fine râles and rhonchi gradually appeared over the lateral aspect of the left lung. *Chest film on Sept. 21, 1955, confirmed the presence of a homogeneous, ill-defined induration of the parenchyma, approximately the size of half a plum, on about the level of the hilum on the left side.* On the same day sulphadimin in full dosage was started alongside with chloromycetin for 24 hours, but since the child still had a high temperature and her general condition was still poor on Sept. 22, the treatment was changed to erythromycin oral suspension only (35 mg of erythromycin per kg of body weight and day). On Sept. 24 this treatment was combined with procaine-penicillin intramuscularly, 300,000 I.U. 24-hourly, since the temperature was still high and erythromycin seemed

to have no effect on the course of the disease. The condition did not improve until Sept. 25, when the temperature fell rapidly from 38.0°C in the morning to 35.6°C in the afternoon. During the next few days she recovered quickly and the findings on physical examination of the lungs became normalized. The progress was uncomplicated. Micro-E.S.R. was 4 mm in 1 hour and *chest film showed no abnormalities on Oct. 4, 1955.*

Discussion

The clinical course of the pneumonia in this case was nearly atypical with the almost negative findings in the nasopharynx, the slightly increased number of leukocytes without any increase in the polynuclears, and the low E.S.R. In addition, there was the raised temperature, the final fall of which cannot with certainty be attributed to the antibiotic agents employed. Unfortunately, the cold agglutinin titre was only determined once, on the seventh day of illness, with a negative result. The child's critical condition during the climax of the disease is no evidence against an atypical pneumonia, since it is well known that P.A.P. in infants is a severe disease which occasionally terminates in death. Virus of the APC group was isolated from the nasopharynx and from faeces on the seventh day of illness. The agent found was identical with Huebner's type 7. There was first a four fold rise in titre in the serum from negative (on the seventh day of illness) to 16 (on the 21st day), and to 32 (on the 118th day after onset) in complement-fixation tests. The convalescent serum contained neutralizing antibodies against the homologous agent, whereas the acute phase serum did not. The simple association of a common virus with an illness does not in itself signify that the virus caused the illness, but it seems to us that the relationship between our patient's pneumonia and the APC virus found is not entirely unlikely.

Summary

APC virus type 7 was isolated from an 8-month-old girl with an atypical pneumonia. Neutralisation and complement-fixation tests showed a significant rise in titer.

Pneumonie atypique chez un nourrisson, associée à une infection par le virus APC.

Le virus APC a été isolé chez une enfant de 8 mois présentant une pneumonie atypique. L'élévation du titre de la réaction de neutralisation, et de la fixation du complément, était absolument probante.

Atypische Pneumonie bei einem Säugling, vergesellschaftet mit APC-Virus-Infektion.

Bei einem 8 Monate alten Mädchen mit einer atypischen Pneumonie wurde APC-Virus isoliert. Neutralisation und Komplementbindungsreaktion zeigten einen deutlichen Anstieg des Titers.

Neumonia atípica en un lactante asociada con infección con virus APC.

En una niña de 8 meses afecta de neumonia atípica fué aislado el virus APC. Los test de neutralización y fijación del complemento mostraron un significativo aumento en sus títulos.

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The Falling Rate of Breast-Feeding in Sweden

by JUSTUS STRÖM

A tendency to earlier weaning has recently become noticeable in many countries. This applies also to Sweden despite its well developed organization for prenatal and infant care.

Fig. 1 illustrates the extent of health control in the country as a whole. The percentage of all infants controlled rose from 82 per cent to 94 per cent between 1944 and 1953. Breast-feeding, by which is meant pure breast-feeding—allaitement mixte being excluded—uniformly shows a falling tendency, barely noticeable for the two-month period but more so at four and six months.

The conditions in respect to different child welfare institutions are analysed in Table 1. In Stockholm, as well as at the centres of Type I in the large provincial towns, the work is led by a paediatrician assisted by specially trained children's nurses. The Type II centres differ only in respect to the doctors, who are not specialists. Rural districts are represented by stations staffed by district medical officers and nurses.

The time when breast-feeding starts to decline noticeably comes, in Stockholm, when the infant is two months old (11 per cent); at provincial Centres Type I there is no decline, and in the remainder of the country the decline is 3 and 4 per cent at Centres Type II and Stations, respectively. At all institutions there is a fairly noticeable decline at four months (6, 5, 4 and 3 per cent). The further decline from four to six months, on the other hand, is fairly moderate (3, 0, 2 and 1 per cent).

TABLE 1

The rate of wholly breast-fed infants at different child welfare institutions 1944 and 1953.

Breast-feeding, months	Centres Type I						Centres type II			Stations			All welfare institutions		
	Stockholm			Other towns											
	1944	1953	Diff.	1944	1953	Diff.	1944	1953	Diff.	1944	1953	Diff.	1944	1953	Diff.
2	85	74	11	74	74	0	74	71	3	79	75	4	77	74	3
4	69	52	17	55	50	5	55	48	7	57	50	7	58	49	9
6	56	36	20	42	37	5	42	33	9	40	32	8	43	33	10

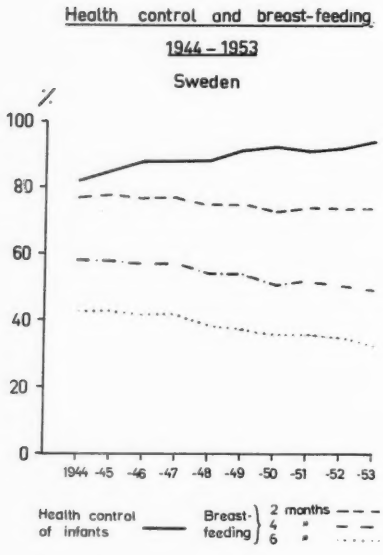

Fig. 1.

Discussion

There may be numerous reasons for the falling rate of breastfeeding, and certain aspects of a more general nature only can be discussed here.

The figure of breast-feeding within the first two months, 74 per cent, must be considered fairly satisfactory, but the development in Stockholm indicates that it could be better. The chief requirement here must be to prolong the period of hospitalizing the mother from the present five or seven days to ten days. In an earlier paper by the author (*Acta pædiat., 35:* 55, 1947), it was shown that with such a measure 92.6 per cent of full-term children (> 2500 g) could be discharged as wholly breast-fed.

The critical four-month limit indicates the existence of special conditions at that stage. It is to be supposed that the mother's job is an important factor. It is at that time that the childbirth benefits to civil servants cease, and the same applies to banks, insurance companies and certain industrial concerns. This would be most noticeable in the large towns and is, in fact, reflected in the figures from Stockholm and other towns with Type I Centres.

Even if these circumstances are of definite significance, it cannot be ignored that there are certain general factors of other kinds. The realization that artificial feeding now involves a negligible risk, the ease of preparing commercial baby foods and the intense propaganda for their use must be potent influences.

Summary

The breast-feeding rate in Sweden has fallen quite considerably from 1944 to 1953 despite the efficiency of prenatal care organization. The rate for wholly breast-fed children under 2 months of age, in the country as a whole, fell from 77 to 74 per cent, under 4 months from 58 to 49 per cent, and under 6 months from 43 to 33 per cent. Certain general causes of this situation are discussed, particular emphasis being laid on the short period of nursing at obstetric departments, women's professions and the financial conditions appertaining thereto, the comparatively slight risks involved in artificial feeding, the ease of using various manufactured preparations and the intense propaganda made for them.

Diminution de l'allaitement maternel en Suède.

L'allaitement maternel a considérablement diminué en Suède de 1944 à 1953, en dépit du développement des organisations de soins prénataux. Le pourcentage des enfants nourris au sein considéré dans tout le pays, a diminué de la manière suivante : En dessous de 2 mois, de 77 à 74 %; en dessous de 4 mois, de 58 à 49 %; en dessous de 6 mois, de 43 à 33 %. Les causes de cette diminution sont ensuite discutées. Un accent particulier est mis sur la période de soins trop courte dans les services d'obstétrique, sur la fréquence des professions féminines et la situation pécuniaire qui en découle, que l'on doit opposer au risque minime d'une alimentation artificielle, à la facilité d'emploi des divers produits diététiques, et à la réclame considérable qui leur est faite.

Die sinkende Frequenz des Stillens in Schweden.

Die Stillfrequenz ist von 1944 bis 1953 in Schweden ganz beträchtlich gesunken, trotz der Tätigkeit der pränatalen Betreuungsorganisation. Die Anzahl der vollgestillten Kinder unter 2 Monaten fiel im Land insgesamt von 77 auf 74 %, bei Kindern unter 4 Monaten von 58 auf 49 % und bei denen unter 6 Monaten von 43 auf 33 %. Gewisse allgemeine Ursachen dieser Situation werden besprochen, insbesondere die kurze Pflegezeit auf der Entbindungsstation, der Beruf und die finanziellen Verhältnisse der Frauen, die verhältnismässig geringen Gefahren, die mit einer künstlichen Ernährung verbunden sind, die Bequemlichkeit der Anwendung verschiedener Fertigpräparate und die für diese intensiv betriebene Propaganda.

Disminución de la tasa de alimentación al pecho en Suecia.

La tasa de alimentación al pecho en Suecia ha bajado considerablemente desde 1944 hasta 1953 a pesar de la eficaz organización del cuidado prenatal. La tasa para todo el país, de niños de menos de 2 meses exclusivamente alimentados al pecho disminuyó del 77 al 74 %, en los menores de 4 meses del 58 % cayó al 49 % y en los de menos de 6 meses del 43 % al 33 %. Se discuten algunas causas generales condicionantes de esta situación, especialmente el corto período de lactancia en los servicios de obstetricia, las profesiones de la mujer y las condiciones económicas como así tabién los pequeños riesgos que involucra la alimentación artificial, la facilidad de usar varios productos manufacturados y la intensa propaganda hecha por sus firmas.

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From the Pediatric Clinic, Bergen University (Chief: Professor ALFRED SUNDAL M.D.)

Anemia Hypoplastica Congenita Treated with Cortisone

Correction of the Anemia with Cortisone Treatment during 4 Years

by ALFRED SUNDAL

In a previous communication Kåss & Sundal[1] have given a report of successful treatment of congenital hypoplastic anemia with ACTH.

The patient, a girl, E. K. N., born on July 29, 1948, showed a severe anemia at 3 months of age, blood transfusion being necessary. Up to the age of about 1½ years the patient needed few blood transfusions to correct the severe refractory anemia, and the clinical symptoms were not quite typical of the diagnosis of congenital hypoplastic anemia before this age. But now the chronic refractory anemia showed a hypoplastic bone marrow involving the erythropoietic elements, and in the peripheral blood there were small numbers of reticulocytes (under 0.3 per cent). From the age of 1½ year the patient needed blood transfusions every 3rd to 4th week; in the following 23 months she received 23 transfusions.

At an age of $3\frac{4}{12}$ years (november 1951) the patient was given ACTH for the first time. She responded rapidly with more reticulocytes and increasing values of hemoglobin and erythrocytes. In the following 14 months (from November 1951 to January 1953) several experiments were performed with ACTH courses and administration of long-acting ACTH, and always the same results were seen: Administration of ACTH increased the number of reticulocytes from below 0.5 per cent to 2–3 and to maximum 8 per cent, the bone marrow altered the picture from a hypoplastic to a normoplastic erythropoiesis, and hemoglobin and r.b.c. showed increasing values. An experiment with long—acting ACTH with one or two injections weekly also gave no relapse of the anemia, and blood transfusions thus became unnecessary. From April 29, 1953 the patient (then nearly 5 years old) and up to the present date (February 1956)—through nearly 3 years—has been given a daily dose of cortisone orally in four doses per day. The maintenance dose of cortisone has been varied. A daily dose of 10 mg seems to be necessary. Doses of 7.5 mg or 5 mg cortisone have for long periods given satisfactory blood values, but with these small amounts, transient and short-lasting febrile diseases (tonsillitis, upper respiratory tract infections) at once have given decreasing values of hemoglobin and r.b.c. But increasing supply of cortisone has at once corrected the anemia. It seems also that she has a greater need of cortisone in wintertime than in the summer. With 10 or 15 mg cortisone orally through the last 3 years her physical

[1] Arne Kåss and Alfred Sundal: Anaemia hypoplastica congenita (anaemia typus Josephs Diamond-Blackfan). Report of a case treated with adrenocorticotropin with effect. *Acta paediat., 42:* 265, 1953.

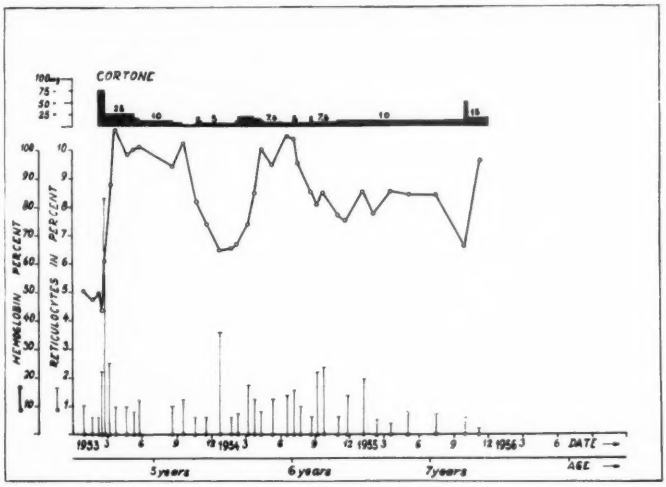

Fig. 1. Girl E. K. N. born July 7, 1948. Hemoglobin and reticulocyte values with maintenance dose of cortisone.

and psychiatric condition has been normal (Fig. 1). In every way she now behaves as other girls and attends school. Her blood pressure has been normal, no "moon-face".

During the last two months we have seen a new case of congenital hypoplastic anemia with a clinical picture and results with cortisone treatment quite similar to our first patient, but the observation period is much shorter.

A girl, K. E., was an only child, born on March 2, 1954, her parents and ancestors being healthy. During the first 4 months of pregnancy the patient's mother was treated with stilboestrol, otherwise no remarks during pregnancy or at birth. Birth weight 2800 g. No untoward events in the newborn period, no icterus. Breast-fed for 3 months, later artifically fed with a normal supply of vitamins.

From birth the mother noted that the child was pale, and as this seemed to increase, the child was examined by a doctor when 2½ months of age. The hemoglobin was then 45 per cent, and as iron administration for two weeks gave no response, the child was transferred to the Children Clinic on June 25, 1954, when 3 months old. Her length and weight were normal. She was very pale, but otherwise nothing remarkable on physical and psychiatric examination. Laboratory tests: Hemoglobin 42 per cent, r.b.c. 1.90 mill., index 1.10. Reticulocytes 2 per cent. White blood corpuscles 4600. Differential counts without remarks. Thrombocytes 220,000. Coombs' test negative. Blood type O, Rh +. Bleeding time, coagulation time and prothrombin time normal. Sodium, chlorides, carbon dioxide and urea in serum normal. Serum iron 175 γ per cent. Bone marrow smear performed three times in the following month gave normal numbers of the erythropoietic and myelopoietic elements. On admission she was given a blood transfusion (120 cc) and two weeks later a second one (120 cc).

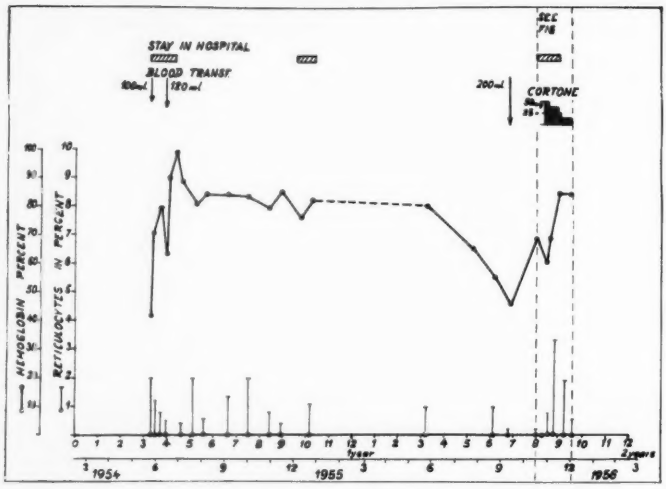

Fig. 2. Girl K. E. born March 12, 1954. Hemoglobin and reticulocyte values during the first 2 years of life.

She was treated with iron, and left the hospital July 22, 1955 with hemoglobin 98 per cent, r.b.c. 4.26 mill. Reticulocytes counted 10 times during her one-month stay in hospital gave values between 2 and 0.4 per cent. The diagnosis was anemia, further classification being impossible (Fig. 2).

During the following 5 months she was at first healthy, but in autumn of 1954 and especially after pertussis immunization she suffered from anorexia and fatigue which increased after 3 days' fever and diarrhoea in December 1954. On January 3, 1955 she was admitted for the second time to the hospital for 3 weeks. On admission nothing noted except a slight anemia. Hgb. 70 per cent, r.b.c. 3.29 mil. Reticulocytes 1 per cent. Without any special therapy the child improved and left the hospital on January 27, 1955 with Hgb. 90 per cent, r.b.c. 3.66 and reticulocytes 1.3 per cent.

Control in the Outpatient Clinic March 1955: Hgb. 64 per cent. In June 1955 Hgb. 66 per cent and reticulocytes 1 per cent. (Iron medication given for about one year was now stopped). Futher 6 controls from August to October 1955 showed falling hemoglobin values from 65 per cent to 46 per cent and r.b.c. from 2.4 to 2.1 mill. She was in October 1955 given blood transfusion (200 cc). Reticulocyte values before the transfusion 0.2 per cent. After transfusion Hgb. 85 per cent.

In November 1955 she was admitted to the Children's Clinic for the third time. The hemoglobin was 69 per cent on admission, but fell to 60 per cent in 6 days. Reticulocyte counts on repeated examination ranged from 0.2 per cent to zero. Bone marrow smear now showed scanty erythropoiesis and the diagnosis hypoplastic anemia was possible. On November 25, cortisone treatment was started: For 6 days 50 mg cortisone daily was given, the following 13 days 37.5 mg, for two days 25 mg, and later 15 mg cortisone daily—the cortisone given in 4 doses per day. The day after cortisone administration considerable increase of reticulocytes up to 5 per cent and gradually increasing values of Hgb. and r.b.c. on discharge from hospital. December 17, 1955 (23 days after corti-

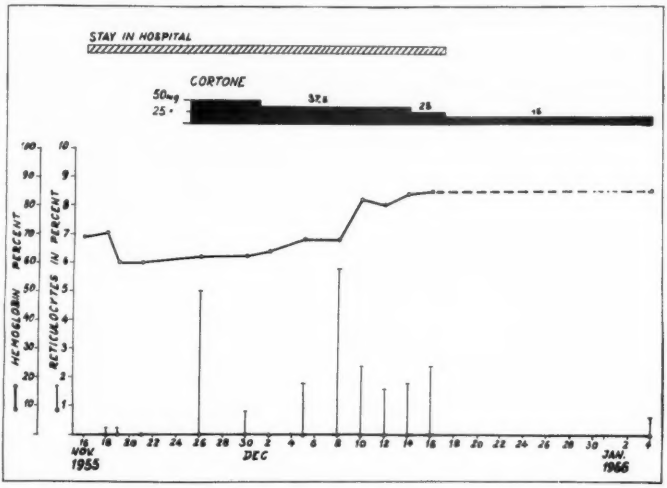

Fig. 3. Girl K. E. (detail of Fig. 2). Hemoglobin and reticulocyte values before and during cortisone treatment.

one treatment): Hgb. 85 per cent, r.b.c. 3.67 and reticulocytes 2.4 per cent (Fig. 3). With a maintenance dose of 15 mg cortisone daily, controls 21/12 1955, 4/1 1956 and 18/1 1956 showed, respectively, Hgb. 85 per cent, 80 per cent and 85 per cent, r.b.c. 2.81, 3.43 and 3.51 mill. and reticulocytes 1 per cent, 0.6 per cent, and 1.2 per cent. (At the control January 4th she had chicken pox.).

Discussion

In the two cases of congenital hypolastic anemia, the anemia started soon after birth, was refractory and needed repeated blood transfusions to be corrected. The classification of the anemia was impossible until about the age of 1½ years, but then reticulocytopenia and hypolasia of the erythropoietic elements in the bone marrow settled the diagnosis. In both cases cortisone treatment gave a promt response, and maintenance doses of 10–15 mg cortisone seemed to prevent relapses (one case observed for 4 years).

It seems from the two cases described here that cortisone contains a factor necessary for the maturation of the erythroblasts to erythrocytes—or that it acts on this maturation process in such a way that the body can maintain sufficient (normal?) formation of red blood corpuscles.

Summary

The author describes and discusses two cases of congenital hypoplastic anemia giving promt response on cortisone treatment.

Anémie hypoplastique congénitale traitée par la cortisone.

L'auteur décrit et discute deux cas d'anémie hypoplastique congénitale, dans lesquels un traitement par la cortisone amena une modification rapide.

Mit Cortison behandelte Anaemia hypoplastica congenita.

Der Verfasser beschreibt und diskutiert zwei Fälle von congenitaler hämolytischer Anämie, die prompt auf Behandlung mit Cortison ansprachen.

Anemia hipoplástica congénita tratada con cortisona.

El autor describe y discute dos casos de anemia hipoplástica congénita que mostraron rápida respuesta al tratamiento con cortisona.

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From The Children's Hospital Fuglebakken, Copenhagen
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Treatment of Nephrosis with ACTH and Cortisone

by FOLKE TUDVAD, M.D.

The question is still open for discussion whether or not nephrosis should be considered a disease *sui generis*. For one thing, the various contesting views are expressed in the nomenclature applied, including: nephrosis; nephrotic syndrome; lipoid nephrosis accompanied or not accompanied by nephritis; nephrotic stage of chronic nephritis; nephro-nephritis; non-specific nephritis; and type II nephritis. But there is also an ever increasing tendency towards including under the diagnosis of nephrosis not only such cases as are characterized by edema, proteinuria, hypoproteinemia, hypo-albuminemia, and hyperlipemia, but also those in which the above symptoms occur combined with hematuria, hypertension, and a reduced renal function.

A series of rather encouraging publications have appeared within the last six years recording the results with treatment of nephrotic children with ACTH and cortisone (1–7, 9–12).

The recorded ACTH dosages range from a daily 50 mg to 100 mg for from eight to ten days (2–5, 7, 9–12), and the cortisone dosage from a daily 100 mg to 400 mg for about ten days. A few of the investigators used an initial brief ACTH treatment and if this provoked a definite diuresis, they continued the treatment with cortisone, either with frequent, small doses continuously (4), or with larger doses administered for three successive days in every week (9).

According to the publications (1–2, 5–7, 9–12), treatment of 188 nephrotic children with ACTH and cortisone had the following effect. Twenty-two (11.7 per cent) were cured; 95 (50.6 per cent) were in remission, i.e. loss of edema, diminution of albuminuria, and improvement in the biochemical findings; 46 (24.5 per cent) of the patients did not respond to the treatment, and 25 (13.2 per cent) died.

In about two thirds of the children the treatment induced a profuse diuresis with a decrease of edema and albuminuria. A simultaneous increase of the serum protein level, in particular of the albumin level, was not unusual, and total serum lipids receded towards almost normal values.

So far it is impossible to decide, on the basis of the available reports, whether ACTH or cortisone should be the preferred treatment of nephrosis, nor can the size of the dosage be finally settled.

Own Results

At The Children's Hospital Fuglebakken, Copenhagen, the diagnosis of nephrosis included even such cases which either (1) had the initial symptoms of a glomerulonephritis and later developed symptoms of a nephrosis, or (2) those which beside the characteristic signs of nephrosis showed hematuria, increase of blood pressure, and reduced renal function.

Since 1951 we have treated a total of 11 nephrotic children; the ACTH or cortisone dosages used have usually been below those stated in literature; the daily ACTH dosage ranged from 10 mg to 30 mg for eight days; the daily cortisone dosage from 100 mg to 200 mg for about fourteen days.

Six of the patients received only a single course whereas the remaining five received either an initial ACTH treatment with subsequent cortisone administration, or repeated cortisone courses. At the termination of the cortisone treatment the dosage was not gradually reduced since the most

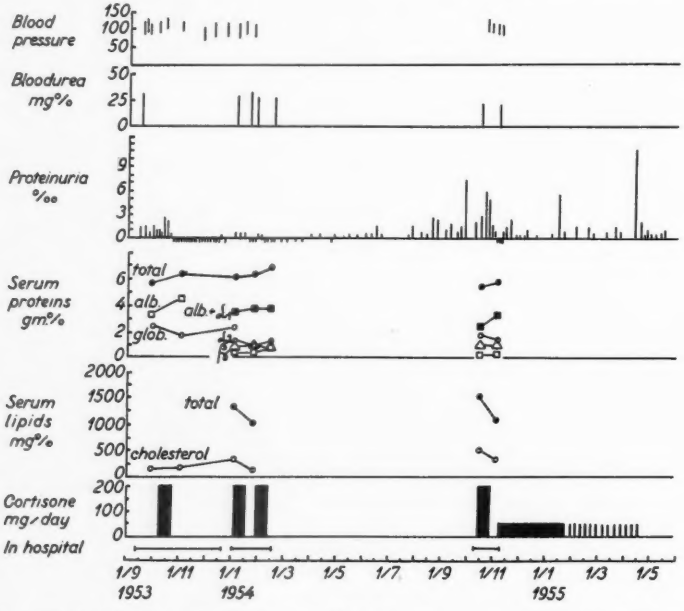

Fig. 1. Biochemical data from a 7-year-old boy during courses of cortisone therapy. Further details in the text.

efficient diuretic effect admittedly is produced through the suddeness with which the drug is abandoned. In two cases the cortisone treatment was continued intermittently, the first patient receiving 100 mg daily the first three days of each of 9 weeks, the other receiving 50 mg daily the three first days of each of 13 weeks.

Fig. 1. shows the course and effect of the treatment in an about 7-year-old boy admitted in September 1953; he had a moderate albuminuria, slight edema, and some diminution of the serum protein level, particularly the albumin level. One month after admission his condition remained unchanged, and 50 mg of cortisone was administered four times a day for fourteen days. The treatment induced a profuse diuresis, loss of edema, and a simultaneous complete disappearance of the albuminuria, together with an increase in the serum protein level. The albuminuria reappeared after three months, but a repeated cortisone course caused a fall in total serum lipids and an increase in the serum protein level. The albuminuria disappeared also, but only to recur shortly afterwards. Again the albuminuria disappeared after a third cortisone course, but reappeared two and a half months later; when the albumin level was at 5‰, edema set in and the child was readmitted seven months after his last hospitalization; cortisone was administered for fourteen days; the albuminuria disappeared with shedding of the edema; the total serum lipids fell to normal values, and there was an increase in the serum protein level. However, the albuminuria reappeared very soon, and 50 mg of cortisone were administered daily for seventy-five days. During the treatment, the urine was occasionally free from albumen, and usually only traces were found. The same cortisone dosage was subsequently administered the three first days of each of thirteen weeks; during this period the albuminuria remained stable at about 1‰ with a single exception; the patient is now attending to his school work without complaints, and for the last six months has received no treatment; the albuminuria remains at about 1–3‰.

Results

A total of five ACTH courses have been given, all of which induced a profuse diuresis; in two cases the albuminuria disappeared but it reappeared in one of them while the other child has had no albuminuria for more than three years. After one of the ACTH courses, the albuminuria diminished from 4 to 0.8‰, but it remained uninfluenced in one child and increased in another after the ACTH treatment.

The serum protein level increased by more than 0.5 g % after one ACTH course, whereas the total serum lipids fell by more than 250 mg% after three of the courses.

Among seventeen cortisone treatments ten induced a profuse diuresis (more than 50%), and three a moderate diuresis. Four courses of cortisone caused a disappearance of the albuminuria, and eight caused a diminution, while three courses failed to influence the albuminuria; in two cases the treatment was followed by an increased albuminuria.

The serum protein level rose by more than 0.5 g% after four cortisone courses; the total serum lipids fell by more than 250 mg% after three of the courses.

The result of the treatments can be summarized as follows: One patient is cured (the period of observation covers more than three years). Five patients are in remission, their albuminuria ranges rather constantly at levels from 0.5 to 1%. They live a normal life without any visible inconveniences; in three of the cases the period of observations covers more than eighteen months. Five patients failed to respond to the treatment.

Side Effects

Neither brief courses with relatively high ACTH or cortisone dosages, nor protracted courses with small cortisone doses induced any side effects in ten of the eleven patients; even their blood pressure remained uninfluenced.

Only one patient exhibited side effects; at the age of three and a half years, a little girl had been treated with cortisone with a satisfactory effect on the diuresis and a diminution of the albuminuria from above 12 to 1–2‰ where it remained for about two years when it rose again to about 9‰ followed by edema and ascites. After an ACTH treatment with four injections of 5 mg daily for one week, the diuresis became profuse; the edema was lost but the albuminuria was not influenced and the biochemical findings did not change. After a ten-day interval, 50 mg of cortisone were given four times a day, but heavy convulsions set in after two days. The serum bicarbonate level was then 17 mM/l; the serum calcium level had fallen to 6.7 mg%; K was normal, but the blood pressure had risen to about 200/140. The convulsions disappeared after large doses of phenemal and intravenous calcium gluconate, and the blood pressure fell gradually to about 150/100. At present, six months after the treatment, the albuminuria is still ranging around 5‰. However, the edema has disappeared, there is no ascites, and she is attending to her school work without any inconvenience.

Among 64 patients Heymann *et al.* observed convulsions in five cases; they have all died later. The occurrence of convulsions after a treatment must be considered an indication of a poor prognosis. Moreover, the above authors found hypertension to be the most frequent complication (11.6 per cent), occurring after ACTH and cortisone, whereas only few cases of hyponatremia and hypokalemia were seen.

Discussion

A favourable effect, at least a temporary one, can be anticipated in 50 per cent of the nephrotic children treated with ACTH or cortisone or a combination of the two drugs.

Only 10 per cent of the children are cured by the treatment; this figure

is hardly an improvement over the number of children cured without any treatment (Kohn & Obrinsky).

However, treatment with ACTH and cortisone makes the existence more tolerable for a number of children who, among other things, will be relieved of their edema; and it cannot be denied that the diminution of the albuminuria may cause a reduction in the number of the complications which would otherwise set in later. So far the periods of observation are too brief to allow any prophesies.

Consequently, it must be considered justifiable to use ACTH and cortisone in the treatment of nephrosis.

Summary

Among eleven children who were treated with ACTH or cortisone or with both drugs (a total of five ACTH courses and seventeen cortisone courses), one was cured (the period of observation covers more than three years); five children were in remission with loss of edema and diminished albuminuria. Five children failed to respond to the treatment. In one patient treated with cortisone convulsions occurred.

Traitement de la néphrose par l'ACTH et la Cortisone.

Onze enfants néphrotiques furent traités par l'ACTH ou la Cortisone ou par l'association des deux médicaments (au total 5 administrations d'ACTH et 17 de Cortisone). Les résultats furent les suivants : Une guérison (la durée pendant laquelle le malade a été suivi est supérieure à 3 ans); cinq rémissions se traduisant par l'absence d'œdèmes et une diminution de l'albuminurie; cinq échecs du traitement. Chez un malade traité par la Cortisone, on a pu noter la survenue de convulsions.

Behandlung von Nephrose mit ACTH und Cortison.

Von 11 Kindern, die mit ACTH oder Cortison oder beiden Medikamenten behandelt wurden (die Gesamtzahl von ACTH-Behandlungen betrug 5, von Cortison 17), wurde eines geheilt (die Beobachtungszeit erstreckt sich über mehr als 3 Jahre;) 5 Kinder waren in Remission mit Verlust der Oedeme und verminderter Albuminurie; 5 Kinder sprachen nicht auf die Behandlung an. Bei einem Patienten, der mit Cortison behandelt wurde, traten Krämpfe auf.

Tratamiento de la nefrosis con ACTH y cortisona.

Se trataron 11 niños con ACTH o cortisona o con ambas drogas (un total de 5 series con ACTH y 17 con cortisona). Uno de ellos curó (el período de observación se extiende a mas de tres años) y 5 mejoraron disminuyendo los edemas y la albuminuria. Otros 5 casos no respondieron al tratamiento. Un paciente de los tratados con cortisona presentó convulsiones en el curso del tratamiento.

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The Geographical Distribution of Iron-Deficiency Anaemia in Childhood

by BO VAHLQUIST

The term *deficiency state* will in the first place suggest vitamin deficiencies of various kinds. During recent years protein deficiency, too, has been attracting keen attention. It is not always realized, however, that *one of the commonest and most important deficiency states is that due to shortage of iron.*

There are various degrees of iron deficiency. Under optimum conditions the body has considerable reserves of iron in the liver, bone-marrow, and spleen. This "depot" iron consists of ferritin or haemosiderin compounds, which are stored in the reticulo-endothelial system and which may constitute up to 40–50% of the iron in haemoglobin, myoglobin, and the iron-containing enzymes. After acute loss of blood it is primarily the depot iron that is utilized for new formation of haemoglobin. If the depots are depleted or exhausted, recovery from the anaemia will be slow and incomplete. The same may occur when extra demands of another nature (rapid growth, pregnancy) are placed on the metabolism of iron and the dietary iron is low at the same time.

The term *latent iron deficiency* is used to describe depletion or exhaustion of the iron depots before any change in the hemoglobin values can be noted. The limit between health and commencing iron deficiency is ill-defined, and the clinical criteria for the degrees of saturation of the iron depots are crude. Direct estimation on a biopsy specimen is rarely possible. A number of indirect signs are recognized, viz. falling serum iron, rising transferrin, increased absorption of iron following oral administration, rapid disappearance from the blood following intravenous injection, and reduced sideroblast count in the bone-marrow. It is not however known at exactly what degree of depot-depletion these signs appear. The findings in certain animal experiments would make it seem probable that the fall in serum iron, for example, does not become pronounced until the reserves are completely exhausted (Hallgren). It is not unusual to see patients, especially

women and young children, with low iron-saturation in the plasma transferrin in spite of haemoglobin values within the normal range. These should be classed as cases of latent sideropaenia.

It cannot, however, be correct to make a diagnosis of latent sideropenia solely on the basis of increase in serum iron following oral administration of iron (cf. Jasinski & Roth). It is indeed true that in iron deficiency absorption of iron increases, but it is also indisputable that an absorption of iron does take place also in subjects with satisfactory iron stores.

Manifest iron deficiency implies that the iron of the heme-proteids is affected; in practice this means lowered haemoglobin iron, since little is known about changes in the myoglobin and iron-containing enzymes, although isolated observations would suggest that these remain unaltered considerably longer than the haemoglobin. The anaemia of iron deficiency is microcytic and hypochromic, and thus has a low "colour index". In many cases other factors causing anaemia are also present, and these may partly mask the characteristic features of pure iron deficiency.

How much is known about the incidence of latent and manifest iron deficiency? For obvious reasons it is to be expected that iron deficiency is comparatively rare in men and much commoner in menstruating women and in young children in whom growth is rapid.

Even under optimum environmental conditions children of 6 months to 2 years exhibit signs of latent iron deficiency. This has been demonstrated both in direct estimations of the liver-iron (N. Smith *et al.*) and in measurements of the iron-saturation of transferrin (C. H. Smith *et al.*; Hagberg). Such a period of latent sideropenia is thus a constant finding, and is independent of environment. When environmental conditions are unfavourable, with prolonged dietary deficiency of iron, blood-loss due to intestinal parasites, and/or anorexia due to protein deficiency or infections, the latent iron deficiency becomes manifest.

In Sweden iron-deficiency anaemia was still common among young children 20 years ago (Vahlquist). With the increasing effectiveness of preventive paediatrics it has become less and less common, and now no longer presents a problem of importance. The same tendency is seen in the other Scandinavian countries.

In England in the 1930's there was a relatively high incidence of anaemia among young children (McKay, Colvert). Here, too, developments have been such that child health has steadily improved and the incidence of anaemia diminished.

The United States is a group of states with varying conditions. Among the coloured population in the South iron-deficiency anaemia still seems to be fairly common, notably among young children (Kaplan).

Iron deficiency constitutes a true national scourge in many of the "underdeveloped" countries. "It represents an important problem which has received less attention than it deserves, possibly because of its relatively undramatic clinical picture" (Jelliffe). Prolonged breast-feeding, a monotonous rice diet, scarcity of iron-rich supplementary foods, and blood-loss due to intestinal parasites constitute the most important causes. The iron deficiency often forms only a part of a general malnutrition, in other cases it predominates in the disease picture. There have been published few series which give a cross-section of the situation in an average child-population, but the following are worthy of note in this connexion.

Stransky & Dauis-Lawas report some figures from the Phillipine Islands.

	No. of cases	Anaemia (< 10.1 g %)	Iron-deficiency	Hook-worm
0–6 months	21+	18	8	0
6–12 months	61	50	50	0
1–2 years	69	52	52	0
2–5 years	28	22	20	1

From the Lady Ridgeway Children's Hospital, Colombo, comes the following summary of haemoglobin values noted in all children admitted during a certain period:

Hb. g/100 cc	No. of cases	% of total cases examined
2–5 g	54	11.7
5–8 g	142	31.0
8–12.8 g	226	49.0
12.8 g and over . . .	39	8.3

It is evident that no less than 42.7 % of the children had haemoglobin values below 8 g %.

Iron-deficiency anaemia *per se* is seldom fatal, but it reduces resistance to other diseases and may result in their taking a serious course. There is no doubt that in this way it has an important effect upon mortality in certain countries. Iron-deficiency no less than rickets belongs to that class of disease which can be prevented by simple means. Iron-deficiency anaemia of childhood in any region can be reduced to a minimum by elementary education and establishment of certain economic and hygienic standards for the entire population.

Summary

Iron-deficiency with anaemia still constitutes in many parts of the world an almost constant finding among young children. The condition lowers the child's general resistance to disease and establishes a vicious circle. Like rickets, iron-deficiency is classed among conditions which can be prevented by improved education and better standards of living.

La distribution géographique de l'anémie par manque de fer.

L'anémie de carence en fer est encore dans certaines régions du monde un fait presque régulier parmi les enfants en bas âge. La maladie réduit la force de résistance des enfants et donne lieu à un cercle vicieux. La carence en fer — de même que le rachitisme — appartient aux maladies qui peuvent être évitées par une amélioration de l'éducation et du standard de vie matériel.

Die geographische Verbreitung der Eisenmangelanämie.

Die Eisenmangelanämie ist heute immer noch in vielen Orten der Welt ein beinahe konstanter Befund bei Kleinkindern. Dieser Zustand senkt die allgemeine Widerstandsfähigkeit des Kindes gegen Krankheit und schafft einen Circulus vitiosus. Genau wie bei der Rachitis ist der Eisenmangel ein Zustand, dem man durch bessere Aufklärung und Erhöhung des materiellen Lebensstandards vorbeugen kann.

Distribución geográfica de la anemia por carencia de hierro.

La deficiencia de hierro con anemia representa todavía en muchas partes del mundo un hallazgo casi constante entre los niños pequeños. Esta condición disminuye la resistencia general de niño contra la enfermedad y establece un círculo vicioso. Igual que el raquitismo la deficiencia de hierro está clasificada entre las condiciones que pueden prevenirse a través de una mejor educación y una mejora del nivel material de vida.

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Chemotherapy in Primary Tuberculosis

by ARVID WALLGREN

Primary tuberculosis is, in itself, a very benign disease in this country. In populations with satisfactory natural resistance, it seldom progresses locally, but even in such populations resistance is at a lower level at two age periods: infancy and adolescence. During these periods local progression may in rare instances develop into primary focus phthisis. In adolescence progressive primary tuberculosis was in former days very rare, because most adolescents had had their primary infection several years previously and primary infection rarely occurred at this age. The further primary infection is postponed from the delicate first years of life to the end of childhood, the more frequent the cases of primary focus phthisis will be occurring in adolescence.

In relation to the total sum of all primary infections, the progressive type of the disease is, however, very rare. The benign cases start, as a rule, as an acute febrile illness after an incubation period of about 6 weeks. The local signs are those of an inflammatory process at the primary focus and the satellite lymphatic glands. It is not the type of radiological findings that is characteristic of primary tuberculosis, but the further progress of the changes. They persist with no sign of regression at a time when acute pneumonias and virus pneumonias already have disappeared. Some years ago, Wegelius and I made a study of the natural course of primary pulmonary tuberculosis in children. We found that the shadows remained unchanged for three to four months, then slowly started to regress in size, at the same time growing more dense and more distinctly limited. After one to two years or a little longer, calcification of the necrotic foci of the primary complex could be seen.

This usually very benign, natural course of primary pulmonary tuberculosis may be interrupted by a hematogenous spread of tubercle bacilli with development of meningitis and/or miliary tuberculosis. This event occurs, as a rule, very early after the manifestation of the primary infection, i.e. within the first 3 months. The younger the infected child, the more frequently meningitis and miliary tuberculosis develop, and they are prevalent

only during the firs t 3–4 years of life. Formerly they were the principal cause of death in infected infants and are still the most dreaded consequences of primary tuberculosis.

What are now the results of chemotherapy in cases of benign primary pulmonary tuberculosis? Comparison of groups of children with primary tuberculosis treated with antimicrobial drugs with groups that have received no such treatment, does not show any definite influence on the rate of regression of the radiological findings and clinical signs. Personally, I have never seen a case that has improved more rapidly by specific treatment, even with high doses, than the untreated children in the study reported by Wegelius and myself. In systemic treatment of tuberculous meningitis one treats at the same time, of course, the other localisations of tuberculous disease, usually a primary pulmonary tuberculosis. Since the acute generalized forms of post-primary tuberculosis, miliary tuberculosis and tuberculous meningitis as a rule develop very early in the course of primary infection, lesions produced by this infection are, generally, recent in children with meningitis. Once the meningitis has been cured by effective chemotherapy, no influence whatsoever is demonstrable on the radiological signs of primary tuberculosis which shows the usual rate of regression.

The reason why specific chemotherapy has no influence on the lesions of primary tuberculosis may perhaps be ascribed to the pathogenesis of these lesions. They are mostly the result of an allergic reaction produced by the tuberculo-toxic antigen of the tubercle bacilli and are not the direct effect of the tubercle bacilli themselves. Necrosis already exists by the time that primary tuberculosis becomes manifest and, usually, does not show a tendency to progression. Chemotherapy can therefore not be expected to diminish the necrotic lesions and probably cannot reach the tubercle bacilli in these lesions.

Bacteriostatic or bacteriolytic chemotherapy of the primary infection before necrosis and allergic reaction have had time to develop, that is during the incubation period, could perhaps be more effective, but this is seldom possible to achieve. Streptomycin, given during the incubation period, has produced a prolongation of this period in experiments on laboratory animals, as well as in man (Olsson-Boje, Lelong *et al.*). We lack knowledge concerning the clinical advantage of such a prolongation of the incubation period.

The aim of chemotherapy in primary tuberculosis cannot apparently be to influence the existing pulmonary lesions. Its task is preventive: on the one hand, prevention of progression of the primary focus to a primary focus phthisis, and on the other prevention of the development of acute generalized forms of postprimary tuberculosis. It has already been stated that progressive primary tuberculosis, at present, is seen but very rarely in early

childhood in this country, while it is not infrequent in adolescence. It is apparently unnecessary to treat childhood primary tuberculosis at ages that never display such a malign course, i.e. in children of pre-school and school age.

The younger the child, the greater is the risk of progression of the pulmonary primary complex. It is evident that those young children should be very carefully watched during the most active phase of the disease, and at the slightest suspicion of progression chemotherapy should be instituted. Experience from abroad has shown that the prognosis of progressive primary pulmonary tuberculosis improves considerably after specific therapy. This experience has led some physicians (Debré *et al.*) to conclude that all infants and small children presenting primary tuberculosis should be given specific chemotherapy in order to prevent or treat, as early as possible, any progression of the pulmonary lesions.

There is certainly less reluctance to admit the desirability of treating early primary infections in adolescents, at least when the infection has led to radiological changes in the lungs. The tendency to progression in this age is apparent not only during the first few months, but for a much longer time. A study that I made some years ago on the development of postprimary pulmonary tuberculosis in adolescence showed that the majority of cases of progressive pulmonary tuberculosis develop during the first year after infection and that almost all cases had occurred during the first three years. I do not believe that it can be recommended to treat every primary infection in adolescence for three years in order to prevent the development of progressive primary tuberculosis. This might be dangerous because of the risk of development of bacterial resistance and of toxic reaction. The treatment might perhaps be confined to that period of primary tuberculosis during which the lesion, from a radiological point of view, seems to be most active, i.e. before it has shown any definite signs of regression. In prophylactic chemotherapy, a limit must be fixed for the period of treatment, as it cannot continue indefinitely.

Above all chemotherapy in childhood tuberculosis has been recommended in order to prevent acute generalized forms of postprimary tuberculosis. Meningitis and miliary tuberculosis arise from a hematogenous spread of tubercle bacilli, and this probably always occurs during the period when the primary infection is manifest. They are most prevalent during the first three months after tuberculin conversion, and occur with rapidly decreasing frequency after this period. Meningitis and miliary tuberculosis are frequent after primary infections only during the first three to four years of life, but show a certain increase at puberty. There is little need to use chemotherapy in the intermediary years of life, at pre-school and school age, in order to prevent meningitis and miliary tuberculosis.

Summary

In my opinion, we must conclude that if chemotherapy is to be used prophylactically in primary tuberculosis, this treatment can be confined to the first three to four years of life and to adolescence. This selection of children to be treated is made from a theoretical point of view from what can be expected of such a treatment. The treatment should preferably continue for three to six months.

La chimiothérapie dans la tuberculose primaire.

Pour autant que la chimiothérapie soit à utiliser au cours de la tuberculose primaire son emploi semble devoir être limité aux 3 ou 4 premières années de la vie, et à l'adolescence. Le choix des enfants auxquels le traitement doit être administré est réalisé par une sélection théorique, se basant sur les résultats que l'ont peut attendre d'un tel traitement. Dans les cas où elle est appliquée, la thérapeutique sera poursuivie de préférence durant 3 à 6 mois.

Chemotherapie bei Primärtuberkulose.

Wenn Chemotherapie bei Primärtuberkulose angewandt werden soll, kann diese Behandlung auf die ersten drei bis vier Lebensjahre und die Adoleszenz beschränkt werden. Die Auswahl der zu behandelnden Kinder erfolgt vom theoretischen Standpunkt mit Hinblick darauf, was von einer solchen Behandlung erwartet werden kann. Die Therapie sollte vorzugsweise für drei bis sechs Monate durchgeführt werden.

Quimioterapia en la tuberculosis primaria.

En el caso de usar quimioterapia en el tratamiento de la TBC primaria, esta debe limitarse a los casos de 3–4 años de edad o a los adolescentes. Esta selección de los casos a tratar está basada en la opinión teórica de lo que de tal tratamiento puede esperarse. La terapéutica debe ser continua durante 3 a 6 meses.

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Congenital Dysplasia of the Hip Joint in Newborn Infants (Luxatio et Subluxatio Coxae Congenita)

by THEODOR WALTHER

During the past 2½ years we have taken a special interest in the dysplasia of the hip joint in the newborn infant. In general, the diagnosis is established relatively late, usually about the time the child starts walking, or a little later. Consequently, the result of the treatment hitherto has not been as satisfactory as it ought to be nowadays.

It is, therefore, of very great importance to diagnose the condition in the course of the first days of life, followed by a treatment which is sufficient and can be finished, in the majority of the cases, before the time the children regularly begin to walk. As regards the newborn babies the main difficulty to overcome is to be sure of the diagnosis, as, to some extent, the common clinical examination of the hip joint at that age is insufficient to discover a dysplasia with subluxation. (A real luxation in a newborn infant is very rare.) Ortolani in 1935 described a symptom now called Ortolani's sign. He maintained that by his way of examining the hip joint he could establish, in nearly 100 per cent of the babies with hip joint dysplasia, a reliable diagnosis of the dysplasia. Hart in his monography stresses the high diagnostic value of this sign. However, he himself did not succeed in demonstrating it in such a high percentage as Ortolani's. The sign is very simple and easy to perform.

The child is put on its back. The knee- and the hip joints are flexed to about 90 degrees, the thighs slightly adducted, inward rotated to about 30 degrees. The thumb of the examiner is put on the medial aspect of the baby's knee, the other 4 fingers spread over the region towards the trochanter major. (From this position the telescope symptom may be demonstrated by exerting a slight pressure from the knee along the shaft of the femur.) From the position mentioned above, the thighs are abducted. In a normal hip joint of a newborn baby abduction is possible to about 80 to 90 degrees. If dysplasia is present, the abduction is limited to 40 to 60 degrees. At this angle an audible, visible and palpable jerk is suddenly observed the moment the femoral head makes its entrance in the socket. Hence, with the head reducted, the abduction in the hip joint is normal. Again, by adduction of the thighs, the jerk may be noticed once more as the femoral head jumps out of the socket.

In the neonatal period asymmetrical skinfolds and creases on the medial aspect of the thighs are of little or no diagnostic help. In case of malformations, especially pes equinovarus, or hyperextension of the knee joint ("position of comfort") the examination of the hip joints ought to be very careful as these conditions are often combined with a dysplasia of the hip joint. It should also be remembered that dysplasia of the hip joint mostly (in about 80–90 per cent) affects females. Roentgen examination may sometimes yield valuable help to the difficult diagnosis of dysplasia with subluxation in the newborn infants.

It is not easy to obtain satisfactory X-rays; moreover, the interpretation of the roentgenograms of the hip joint may be extremely difficult. As the child grows older, and the development of the centre of ossification of the femoral head takes place, the roentgen examinations are of paramount importance for the evaluation of the dysplasia itself and the results of the treatment. In a normal child, however, there is a very wide variation concerning the time when the centre of ossification appears.

In the course of the period beginning 1/5 1953 and ending 31/12 1955 all children born in the Maternity Hospital in Bergen were clinically examined with a view to dysplasia of the hip joint. The total number investigated amounted to 8260 children. Their age varied from 1–3 days at the moment of examination. The clinical diagnosis was based on the presence of the Ortolani's sign. Thirteen cases of dysplasia with subluxation were discovered. The sex distribution was 12 females and 1 male. In 7 children Ortolani's sign was bilateral, and in 5 unilateral, while one baby presented the telescope symptom only. In two clinically unilateral cases the roentgen examination revealed a bilateral dysplasia. All the cases were classified as follows: In 9 children the dysplasia was bilateral and in 4 unilateral.

One child, in addition to the dysplasia, had a pes equinovarus and a dysostosis cranii and would not thrive. Another baby had a chondrodystrophia calcificans punctata, and a third one presented a hyperextension of the knee joint. In that baby it was quite easy to demonstrate the intrauterine "position of comfort": With the left lower limb hyperextended at the knee joint and flexed at the hip the extremity could easily be bent upwards in front of the chest with the child's foot at the shoulder. In the remaining 10 children nothing remarkable could be elicited.

A father of one child and a mother of another baby were affected with luxation of the hip joint.

The frequency of dysplasia of the hip joint among Norwegian children thus amounts to about 0.16 per cent. However, 3 further children with negative Ortolani's sign when examined as newborn babies in the period mentioned above, revealed dysplasia of the hip joint when reexamined at the age of 7 weeks, 4 months and 8 months respectively. Reexamination of the other 8244 children without clinical signs of dysplasia as newborn babies has not yet been done.

The treatment, starting in all cases before the child was one week old, has followed the principles mentioned below. The lower limbs are flexed at the knee- and the hip joints. The thighs are rotated slightly outward, and abducted at the hip joints until the femoral head enters the acetabulum. The majority of the children has solely been treated in Frejka's splint, 3 for a shorter period in Chapple's position, followed later on by Frejka's splint, the latter of which in my experience is the treatment of choice.

The earlier cases of ours were treated for about 9 to 10 months, but in the course of the last year the time of treatment in Frejka's splint has been reduced to 5 to 7 months, followed by gentle exercise given by a physiotherapist. During treatment in the splint, monthly roentgen controls have been done. A close observation is necessary until the child starts walking, and further up to the age of 2 years or even longer as the children for some time walk clumsily on a wide base with the legs apart. Up to the end of 1955, three children treated for about 5 months in the Children's Clinic have been transferred to an orthopedic hospital, as the result of our treatment was unsatisfactory. One child with a different kind of malformations died at the age of one year. Four have started walking between 14 to 19 months of age, and the gait is now quite normal and the hip joints show normal roentgenologic conditions. The other children are still under our observation and treatment.

Summary

Based on the clinical examination of the hip joints of 8260 newborn babies the author discusses the diagnosis of the congenital dysplasia of the hip joint. He stresses the importance of Ortolani's sign. He discovered 13 cases, 12 girls and 1 boy. He prefers the treatment in Frejka's splint for 5–7 months.

Dysplasie congénitale de la hanche chez des nouveaux-nés.

L'expérience de l'auteur basée sur l'examen clinique de la hanche chez 8260 nouveaux-nés, lui permet de discuter le diagnostic de dysplasie congénitale de la hanche. Il attire l'attention sur l'importance du signe d'Ortolani. Il a pu ainsi découvrir 13 cas (12 filles, 1 garçon). Il préfère le traitement par la mise en position de Frejka durant 5 à 7 mois.

Congenitale Dysplasie des Hüftgelenkes bei Neugeborenen.

Gestützt auf die klinische Untersuchung des Hüftgelenkes von 8260 Neugeborenen bespricht der Verfasser die Diagnose der congenitalen Dysplasie des Hüftgelenkes. Er betont die Bedeutung des Ortolani'schen Zeichens. Er entdeckte 13 Fälle, 12 Mädchen und 1 Knaben. Er bevorzugt die Behandlung in der Frejka'schen Schiene für 5–7 Monate.

Displasia congénita de la cadera en recién nacidos.

El autor discute el diagnóstico de displasia congénita de la cadera basandose en el exámen clínico de 8260 recién nacidos. Se llama la atención sobre la importancia del signo de Ortolani. En el material revisado fueron encontrados 13 casos, 12 niñas y 1 niño, de esta afección. El autor prefiere el tratamiento con férula de Frejka durante 5–7 meses.

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From the Children's Department and the Out-Patient Clinic for Children with Allergic Diseases, Rigshospitalet, Copenhagen (Chief: Professor PREBEN PLUM, M.D.)

Recurrent (Allergic?) Swelling of the Parotid Gland

by KNUD WILKEN-JENSEN

Recurrent swelling of the parotid gland seems to have been neglected by Scandinavian authors. The only description of it in the Scandinavian literature is from 1912 (Lange) and in that case the author wanted help to get the diagnosis.

Kussmaul reported, in 1879, a patient with this condition and compared the disease with "bronchitis fibrinosa", and since then a number of cases has been published under the name of "sialodochitis fibrinosa".

The first to report the condition in children was von Reuss (1909), and he was also the first to find eosinophilia in the blood of such a patient.

In 1913 Heineke gave an extensive survey of the literature of this and similar conditions and, although the descriptions of the different patients vary a great deal, Heineke felt that the pathogenesis of many of the recurrent swellings seemed to be the same and he regarded "angioneurotic oedema" of Stenson's duct as the most probable cause, and if infection was present, he believed it to be secondary.

Bruce Pearson (5, 6, 7)—who has reported more cases than any other author—found that "although infection was the commonest cause of recurrent swellings, a number of my patients had evidence of an allergic basis for the condition, notably the presence of asthma or other allergic disease, in the patients or their families, and the presence of eosinophils in the parotid secretion" (personal communication).

In 1952 the disease was dicussed in the American Pediatric Society, but no conclusion is reported. American allergologists, however, now use the name "allergic parotitis" for the condition (10, 11).

By reviewing the literature on recurrent parotid swelling, it is very difficult to be certain of the relative importance of allergy and infection. When bacteria are cultured from the saliva, it is impossible to know whether the infection is the primary cause of the swelling or if it is secondary. Only one case has been followed for three years before infection took place (1).

The characteristic symptoms—in favour of the allergic theory—are:

1) The very often acute onset of swelling which may take only a few minutes, so that it is difficult to find any other explanation than an allergic oedema. It may last for minutes, hours or days. It may leave no trace at all or a little enlargement, especially after several attacks.

2) The recurrence which may take place in one or both parotid glands or alternatingly in any of the salivary glands (Meyer).

3) The saliva which may be normal, i.e. clear and serous, but it may contain eosinophils in great number. It may also be mucous or "ropy" and contain flakes or plugs or a Charcot-Leyden's crystal (Kussmaul). The swelling may be explained by oedema, spasm or a plug of mucoid or fibrinous or purulent material in Stensen's duct or its branches or a combination of these causes. (Sialolithiasis can be excluded by X-ray).

4) Allergic symptoms may be present in the personal history or in the family. In some patients the parotid swelling occurs together with definite allergic symptoms, in others in addition to abdominal pains or colics whose allergic nature is difficult to ascertain. In some instances the swelling is preceded by an infection or it occurs during the menstruation. This may be due to an infection allergy or an allergy towards the female hormones, or it may be explained thus: the patient can suppress his allergic reactions under normal circumstances but when his resistance is lowered for some reason or another, he cannot control his allergy. Only in a few cases has the provoking allergen been detected. In such cases elimination and hyposensitization have given good results (4, 7, 10, 11).

5) Eosinophilia may be found in the blood.

The appearance of the affected gland and the unpleasantness it involves vary greatly and are not characteristic. The gland is seldom really painful, the skin above it is usually pale and cool, but in cases with infection it may be red and hot. The inconvenience of the condition is often only disfiguration of the face and the suspicion of mumps which it may cause.

The sialogram shows the site of the obstruction and the dilatation of the duct or branches and says nothing of the cause. Dilatation of the terminal ducts seems to be most frequent in children.

Two case histories:

1. Boy H. J. 1056/51. No allergy in personal or family history. Two years old he started having attacks of recurrent tumor of the parotid glands alternatingly, 8 times in 3 years. Onset sudden and perhaps accompanied by a slight fever. When seen 5 years old the right parotid region was rather firm, tense, red and tender. Four months later a new swelling of the same gland occurred. The saliva was mucoid with small particles which contained myriads of eosinophils. Nine months later a further attack took place and again the saliva contained eosinophils. The attacks were preceded by slight infections. Different bacteria were cultured from the saliva. The sialogram showed

slight dilatation of terminal ducts. B.S.R. on one occasion 25 mm/1 hour. Apart from this, nothing of importance was found. Skin tests were negative. Each attack lasted about one week. The swelling disappeared without treatment.

2. Girl S. N. 684/52. Born with embryopathia rubeolica, including cor biloculare, vena cava superior duplex, neurolabyrinthopathia acustica duplex and chorioiditis diffusa. From the age of 2, she had recurrent swelling of the left parotid gland, lasting 4–5 days, always in connection with a cold or another infection (measles). At nearly 7 years of age her heart was catheterized and 3 days later the swelling recurred. The whitish, almost granular saliva was filled with eosinophils. Skin tests were negative. Nothing abnormal in laboratory findings. Sialography showed enlarged acini. When seen 2 years later she had had one recurrence in connection with a common cold.

These two cases exhibit acute swelling after infections and the latter also after an operation. None of them have allergy in their history or in the family. Their skin tests are negative. None have eosinophilia, but both of them have lots of eosinophils in the saliva. In the girl the tumors always occur in the same gland, in the boy both parotid glands may be affected alternatingly.

Summary

The literature is shortly discussed and the symptomatology of recurrent swelling of the parotid gland is related. The problem of pathogenesis is simultaneously discussed especially with regard to allergy. Two cases are reported.

Hypertrophie récidivante de la parotide.

La symptomatologie de l'hypertrophie récidivante de la parotide est rappelée, et une rapide revue de la littérature est discutée. Le problème de la pathogénie de l'affection est envisagé, notamment ses rapports avec des phénomènes allergiques. Deux cas en sont rapportés.

Wiederholte Schwellung der Parotisdrüse.

Die Literatur wird kurz besprochen und die Symptomatologie der wiederholten Parotisschwellung berichtet. Gleichzeitig wird das Problem der Pathogenese, insbesondere mit Rücksicht auf die Allergie, erörtert. Zwei Fälle werden berichtet.

Tumefacción recurrente de la glándula parótida.

Se discute brevemente la literatura al respecto y se relata la sintomatología de la tumefacción periódica de la parótida. El problema de la patogenia se enfoca principalmente en su relación con la alergía. Se comunican 2 casos.

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From the Children's Castle and the Children's Hospital, Helsinki University

Chronic Cerebral Fever in Cerebral Palsy

Temperature Athetosis

by LEA YLPPÖ and ARVO YLPPÖ

Peculiarly prolonged febrile conditions of several months' duration, either uninterrupted or intermittent, are often encountered in the Children's Castle of Helsinki where, in addition to other patients, some 160–180 "cerebral palsy" patients are treated annually, their daily numbers varying from 50–60. The primary cause of these febrile conditions often seems to be a mild infection, e.g. influenza in the ward. But as they then stubbornly continue from month to month, often as a high intermittent fever with no specific inflammatory local symptoms to account for it, we have introduced the term "cerebral fever" or "temperature athetosis" to describe them.

Our experience suggests that we might attribute these febrile conditions and changes primarily to the various brain lesions of the cerebral palsy patients. These lesions may be highly diversified in type, and, similarly, the originating mechanism of the fever may be very complicated. When such children succumb and are autopsied, we have frequently failed to find anything indicative of an acute cerebral process, acute meningitis, encephalitis or cerebral abscess. In some cases the brain may even show a macroscopically almost normal appearance, in others cortical changes with some cicatricial changes, both atrophy and sclerosis of the gyri, atrophy of the basal nuclei and hydrocephalic changes. These cerebral findings and the connected histological changes as well as the whole problem will be reported in greater detail later.

Here we only wish to draw attention to the peculiar phenomenon and its clinical manifestations by describing the following two typical examples.

Case Reports

Case I.—Child E. Bl., a girl born Jan. 6, 1955, of healthy parents. The family had 3 children. The eldest, a son, breech presentation, was born March 9, 1950, birth weight 2200 g. The child has typical Little's disease, learned the rudiments of walking at the age of 4 only, has a disturbed mental development but is able to talk. Suffered often from fevers associated with convulsions. The fevers usually disappeared after a few days. The second child, a girl was born 1953 and is healthy.

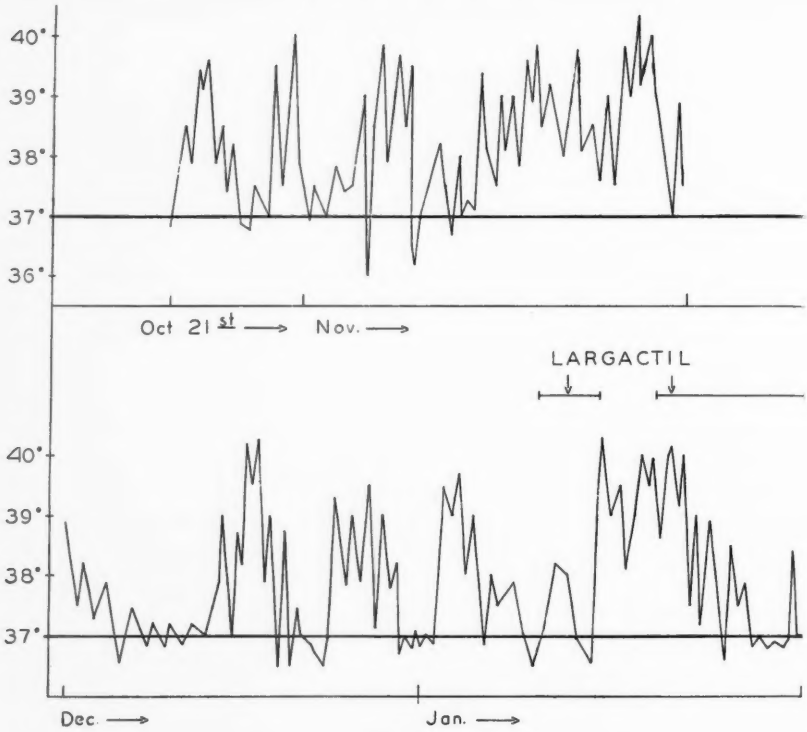

Fig. 1.

The patient, the third child, a girl, was a *premature breech presentation*, birth weight 2350 g. She was brought to the Children's Hospital at the age of 4 days for laboured breathing and sleepiness. Lumbar puncture: Liquor yellowish, fairly turbid, bact. −, Nonne +, Pandy +, Leuc. 4, Erythr. 6100. She was sleepy and limp. No spasticity or paresis of the extremities was noted on this occasion. Subdural puncture: right side negative, left side gave some drops of yellowish liquor with a few blood cells. The child's development retarded and slow. *Spasticity* developed gradually in all the extremities and her weight increased poorly. She was readmitted to the Hospital September 15, 1955, after sudden cyanotic attacks which made her turn blue and begin to cry. *Evident tetraplegia* and general rigidity were noted. Her mental development was somewhat retarded, but she was able to follow with her eyes. The head was not enlarged; the tension of the fontanelle was somewhat elevated. No stasis was found in the ocular fundi. The patient was transferred to the Children's Castle on Sept. 28, 1955. *From Oct. 21 until February 1956 she has persistently had fever between 37–40°C* (see Fig. 1). No factor to account for the fever can be traced. The antibiotics and certain antipyretics seem to have no effect on the fever; only with cold baths of 30–33°C can the temperature be reduced temporarily. Largactil seems to have some reducing effect on the fever, as can be seen from the attached curve.

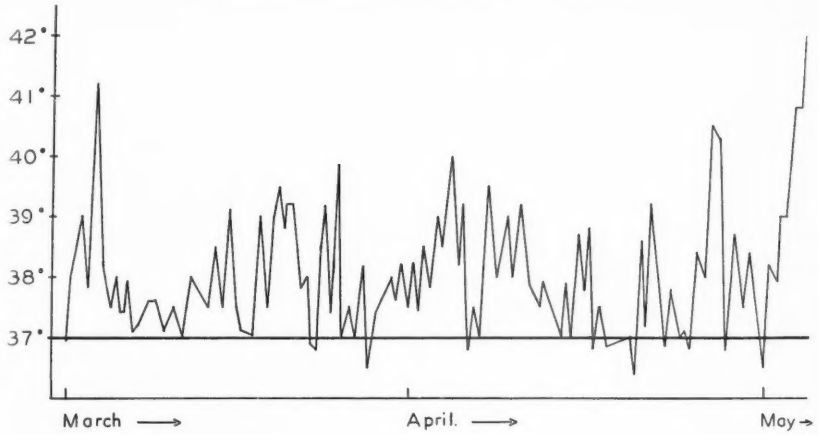

Fig. 2.

The lungs were roentgenologically normal, with no enlarged glands. In spite of the high fever, the child's general condition is not particularly alarming, and she is not especially anaemic. During the feverish stage the liquor is clear. Pandy and Nonne −, and cell count only 1–3. No special haematologic changes, e.g. leucocytosis, are found during the fever. Considering the highly febrile condition, the anaemia remains relatively slight. For instance, the last blood picture of Feb. 1, 1956 was: Hgb Sahli 62/70, Er 3.54, Leuc. 5700, Lymph. 55 %, Sedimentation rate only 12. (*Comment on proof-reading:* This highly febrile condition continued until her death on April 19. Post-mortem examination: Brain: The right hemisphere smaller than the left. Microgyria in both Lob. frontal. In Hypothalamus and Corpus striatum small white spots, dispersed cicatrices. Tracheobronchitis levis.)

Case II.—E. P., a boy, born July 16, 1952. One of twins, birth weight 2650 g, *forceps delivery*, in a state of suspended animation, second day strongly icteric. His development was fairly slow, but he followed with his eyes and prattled. He was admitted to the Children's Castle March 1, 1954, after suffering from prolonged fever at home. Auscultation revealed some moist râles over both lungs, for which reason pneumonia was suspected on admission. Thorax roentgen, however, showed no shadows. The râles disappeared, the fever persisted. No special findings on lumbar punctures (see Fig. 2).

Antibiotics and antipyretics did not affect the temperature rises. Before his death he contracted a cough and his temperature rose to higher peaks than before. He died May 4, 1954.

Post-mortem examination gave no special macroscopic findings of the brain; the lungs were soft. Diagnosis on autopsy: Oedema pulmonum. Hyperplasia lymphonodos. colli et mesenterii. Tracheobronchitis.

Persistent febrile conditions of this type, which we have been unable to explain clinically, have been noted in some 5–10 per cent of our cerebral

palsy patients, to a varying degree in different years. In the last two years, 10 of these febrile patients have died. Even though their post-mortem examinations have revealed certain catarrhal bronchial or lung changes, the changes may in part have been preagonal, and, in our opinion, they cannot account for febrile conditions of several months' duration like these. Although our histologic brain studies have not yet been completed and will be reported later in another context, it does not seem likely that they will be able to provide a clear solution to the etiology of these prolonged febrile conditions.

It is considered a proven fact at present that normally the hypothalamus is the most important centre of thermal regulation in man. Hence it might be assumed that in these febrile conditions the hypothalamus is defective in some special way. Some of the autopsies have in fact revealed pathologic changes in the hypothalamus (Case 1) and also atrophy of the basal nuclei, especially in cases with a severe Rhesus factor immunization and severe kernicterus in the earliest days of the child's life.

However, we must remember that, even with lesions in the area of the hypothalamus, the thermal regulation need not necessarily be as inadequate as it appears to be in the children now in question. The thermal regulation of the hypothalamus can be replaced by other organs and sections of the brain and even of the spinal cord, as the most recent physiologic research has shown (Hensel). Hence it is evident that no really far-reaching conclusions can be drawn from the relationship of the temperature rises with an exactly defined and localized brain lesion.

Incidentally, it is a known fact that *adults with hemiplegia very often show hyperthermic conditions* attributable to vasoconstrictive disturbances of the damaged brain sections.

The brain lesions of the cerebral palsy children are highly diversified, as are their clinical pictures. We distinguish between spastic, athetotic and ataxic types. They are also often considered to result from brain lesions of a certain localization. But we know from experience that classic clinical pathologic pictures are as rare as the corresponding classic localizations of brain lesions. We have noted that *most of the febrile spastic patients under consideration have had athetosis in addition to spasticity.*

It could be assumed that, in these spastic-athetotic patients, the thermal regulation and the *defective brain* regions governing it *react to certain stimuli by temperature rises reminiscent of athetosis and not calculable in advance.* The initial impetus for this sudden soaring of the temperature might come from a most varied range of infections, either general or local. *Once such a defective thermal regulation becomes unstable, the pendulum-like swings may continue for months.* In addition to infectious factors, both motor and

psychic tensions in children with a labile thermal equilibrium may also cause pendulum-like swings.

Naturally, chronic cryptogenic septic states or chronic inflammations of glands with intraglandular suppuration might also be assumed in such cases. One of the authors (A.Y.) has published a case where post-diarrhoeal suppuration of the mesenteric glands of a patient with myatonia congenita resulted in high intermittent fever of several months' duration. However, in this case as in most of the cases in the last mentioned group, there are definite signs indicative of infection, e.g. increased leucocyte counts, which were missing in many of our cases.

From all this we are inclined to ascribe these febrile conditions of the cerebral palsy patients primarily to a brainbased disturbance of the thermal regulation and to compare them with the typical motor athetosis.

Summary

Children affected with *cerebral palsy* relatively often show *chronic intermittent febrile conditions persisting for months*, conditions which cannot be ascribed to chronic infections alone. The authors consider that a so-called *cerebral fever* is involved, arising from a disturbed thermal regulation resulting from brain lesions.

The condition is comparable to the motor athetosis of cerebral palsy children and could be termed *temperature athetosis*. Neither antibiotics nor antipyretics seem to have an effect on this fever.

Fièvre cérébrale chronique au cours des paralysies d'origine cérébrale.

On peut souvent noter chez des enfants atteints de lésion cérébrale, une fièvre intermittente et chronique persistant plusieurs mois. Cette hyperpyrexie ne peut cependant être mise sur le compte d'infections chroniques. Les auteurs l'attribuent à une fièvre d'origine cérébrale, qui serait le résultat d'une dysrégulation des centres thermiques, provoquée par des lésions cérébrales. Cet état est analogue à l'athétose des enfants atteints de paralysies cérébrales, et peut être appelée « température d'athétose ». Ni les antibiotiques, ni les antithermiques n'ont d'action sur cette hyperpyrexie.

Chronisches cerebrales Fieber bei cerebraler Kinderlähmung.

Kinder, die mit cerebraler Kinderlähmung behaftet sind, zeigen relativ häufig chronisch intermittierende febrile Zustände, die monatelang bestehen, Zustände, die nicht allein chronischen Infektionen zugeschrieben werden können. Der Verfasser glaubt, dass ein sogenanntes cerebrales Fieber beteiligt ist, das aus einer durch Hirnschäden gestörten Thermoregulation resultiert. Der Zustand ist der motorischen Athetose cerebralparalytischer Kinder vergleichbar und könnte febrile Athetose genannt werden. Weder Antibiotica noch Antipyretica scheinen einen Einfluss auf dieses Fieber zu haben.

Fiebre cerebral crónica en la parálisis cerebral.

Los niños afectos de parálisis cerebral muestran amenudo períodos de fiebre intermitente de varios meses de duración, condiciónes que no pueden ser atribuídes solo a infecciones crónicas. Los autores consideran que una fiebre cerebral tiene lugar originándose en un trastorno de la termorregulación como resultado de lesiones cerebrales. Dicha condición es comparable a la atetosis motora que sufren estos enfermos, pudiendo llamarsela atetosis de la termorregulación. Ni los antibióticos ni los antitérmicos parecen tener efecto contra esta fiebre.

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Urinary Excretion of Amino-Acids and Sugar in the Nephrotic Syndrome

A Chromatographic Study

by L. I. WOOLF and H. McC. GILES

This investigation was prompted by the discovery in a young infant with the nephrotic syndrome, but with certain features suggesting cystine storage disease, of marked amino-aciduria[1] and glycosuria. Twenty-nine children with the nephrotic syndrome were subsequently studied by paper chromatography and many were found to have amino-aciduria and glycosuria: these observations are the subject of the present communication.

Amino-aciduria, augmented by feeding protein hydrolysate, was noted in two nephrotic patients by Milhaud and Courvoisier (1951) and Martin and Milhaud (1952). Later Squire (1953) and his colleagues (Blainey) observed glycosuria and amino-aciduria in adult patients; Blainey also quotes Glagov as describing amino-aciduria in 3 cases. Shreeve *et al.* examined the urines of two adult patients by microbiological assay, and found in one a marked and in the other a slight increase in the excretion of a number of amino-acids. Plückthun *et al.*, also using microbiological assay, found increased concentrations of some amino-acids in the urine of 5 nephrotic children, though the total 24-hour output was within the normal range. Durand examined chromatographically the urines of 10 children and found quantitative and qualitative abnormalities of amino-acid excretion. On the other hand, Slater *et al.* found no evidence of amino-aciduria in 10 children with the nephrotic syndrome.

Glycosuria has long been recognised as a feature of nephrosis (Hawkins *et al.*), but is often overlooked.

Material

The subjects studied all presented at some time in their illness the characteristic features of the nephrotic syndrome, namely, oedema, gross albuminuria, hypoalbuminaemia, hyperlipaemia, and minimal haematuria. Hypertension and azotaemia

[1] The term "amino-aciduria" is used to imply an abnormal increase in the urinary excretion of amino-acids and, in some cases, of related amino-compounds.

were inconstant but were more marked in patients who died. No specific aetiology was identified in any case except insofar as some showed terminal or autopsy evidence of glomerulonephritis. There were 18 boys and 11 girls; their ages at the time of observation ranged from 8 months to 14 years and the period for which they were under observation from 3 months to 7 years. Eight children ultimately died, 8 still have unequivocally active disease, 4 have slight albuminuria but no other abnormality (except for hypertension in one case) and 9 have been in remission for at least 6 months.

In all 70 urine specimens were examined for amino-acids and 64 for sugars; the majority of these were single specimens obtained 1 to 3 hours after ingestion of a mixed meal, but 15 specimens from 8 subjects were 12- to 24-hourly collections. In addition, 7 blood samples from 5 subjects were examined for amino-acids by paper chromatography.

Methods

Urine specimens were preserved with chloroform or chlorbutol and refrigerated during the time between collection and examination, which was generally a few hours, but sometimes two to three days. The serum from venous blood was used for examining blood amino-acids.

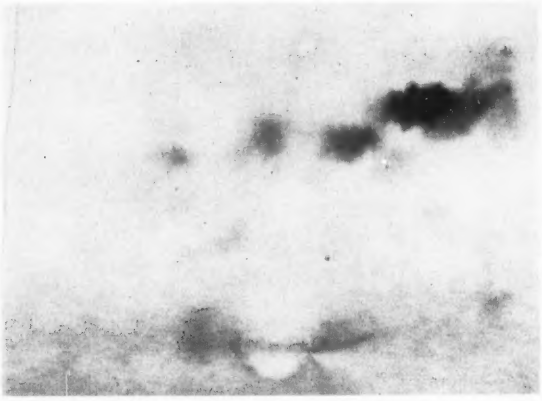
Specimens were prepared for amino-acid chromatography either (a) by precipitation with trichloracetic acid in the cold, extraction of trichloracetic acid with ether, and electrolytic desalting, or (b) by passage of urine or serum through a column of Zeo-Karb 225 (a sulphonated polystyrene resin, 12 per cent crosslinked, in the form of beads about 0.5 mm diameter), removal of protein, sugars and other non-basic solutes with water, and finally elution of amino-acids off the resin with 5*M* ammonia.

For sugar chromatograms method (a) was used, but instead of electrolytic desalting, the ionisable substances were removed with the mixed bed resin Biodeminrolit-G (Woolf, 1953). The deproteinised urine or serum was examined for amino-acids by two-dimensional paper chromatography and for sugars by one-dimensional paper chromatography (Consden, Gordon and Martin; Woolf, 1951).

The amount of urine used for an amino-acid chromatogram was determined by measuring the creatinine concentration of the specimen, and taking a volume bearing an inverse relationship to this concentration (Woolf, 1951). A constant volume of serum was used. For the estimation of sugars, a known volume of urine was used and the spots compared with those from known amounts of sugars run on the same chromatogram. The chromatograms obtained were assessed by comparison with over 2500 chromatograms of urine and blood from healthy children and children suffering from various diseases.

Results

Of the 28 subjects whose urinary amino-acids were investigated, 25 showed an abnormal excretion at some phase of their illness. Of the individual urine specimens, 13 gave amino-acid chromatograms that fell within the normal range while the other 57 contained increased amounts of some amino-acids and so gave abnormal chromatogram patterns. Most of the abnormal chromatograms could be allocated to one or other of two groups. In the first (referred to in the tables as "R"), the pattern approximates to that of normal



ig. 1. Paper chromato-
am of the amino-acids
the urine of a normal
child.

Fig. 2. "R" pattern: paper chromatogram of the amino-acids in the urine of a child with the nephrotic syndrome (E. B., 23.4.53). The outline of the spots due to proline and hydroxyproline were marked on the chromatograms with dotted lines and the spots marked "P" and "HP" respectively.

blood, with proline, leucine, valine and alanine predominating (Fig. 2); a similar pattern has been repeatedly seen in renal failure from divers causes (Woolf, 1951). The other group (referred to in the tables as "H") is characterised by increased excretion of ethanolamine, β-amino-isobutyric acid, taurine, tyrosine, leucine and valine, recalling the pattern found in such conditions as hepatic dysfunction associated with derangement of amino-acid

Fig. 3. "H" pattern: paper chromatogram of the amino-acids in the urine of a child with the nephrotic syndrome (E. O'B., 3.6.53).

intermediary metabolism (Fig. 3.). Within the two classes there were wide variations in the total amounts of amino-acids present, and, in the case of the "H" pattern, in the relative amounts of the different amino-compounds. A few of the "R" type chromatograms also showed moderate increases in the amounts of ethanolamine and β-amino-isobutyric acid, suggesting some admixture of "H" in the predominant "R" patterns in these cases; similarly, some of the "H" pattern chromatograms also showed elements of the "R" pattern. The two specimens of urine from patient H. C. showed a marked amino-aciduria intermediate between "R" and "H" in type.

The results of individual urine examinations, and the outcome of the illness in relation to the type of amino-aciduria are summarised in Tables 1 and 2 respectively. Three patients who have been observed for less than 6 months are excluded from Table 2. Of the 3 patients showing no amino-aciduria, 1 had only minimal albuminuria at the time of investigation, and 1 was in complete remission, while the third patient subsequently made a rapid and complete recovery. Thirteen patients showed the "H" pattern but not the "R" pattern; these include 2 of the cases already mentioned who have been observed for less than 6 months.

Of the other 11 patients in this group 2 have died, 1 still has manifest nephrosis, 2 have albuminuria without other evidence of activity and 6 have been in complete remission for from 6 months to 2 years. In 3 patients the "R" pattern was found but not the "H" pattern, and 9 patients showed

TABLE 1

Patient	Sex	Date of onset & age at onset (yrs.)	Date	Urine			Clinical Condition
				Amino-acids	Glucose mg/100 ml	Fructose mg/100 ml	
R. A.	M	May 1951	28.11.52	h	0	0	A
		4	29.3.55	h	0		A
			24.10.55				A
E. B.	F	Sept. 1951	28.11.52	HH	150	15	N u
		5	12.12.52	H	150	15	N u
			23.4.53	RR	400	10	N u
			23.4.53	RR	800		N u
			7.2.55	normal	10	6	?N u
			25.4.55				Died
A. B.	M	Apr. 1953	20.8.53	Rh	250	12	N t
		9	17.12.54	h	0	0	N t
			15.4.55		0	0	?N t
			29.12.55	h	5	7	A
R. B.	M	Dec. 1952	10.3.53		2	0	N t
		$2\frac{1}{4}$	1.2.55	normal			A
			29.3.55	normal	10	10	Rem
			8.11.55				Rem
S. B.	M	Born 20.3.47	3.9.52	H	40	0	N
		?	17.1.53	H	30	10	N
			28.3.55	RR	300	25	N
			3.12.55	RR	150	8	N
B. B.	M	Apr. 1952	19.6.53	H	2	10	N t
		$5\frac{1}{2}$	4.5.55	RR	100	15	N t
			14.12.55	RR	400	30	N t
H. C.	F	Sept. 1952	6.2.53	HR	0	0	N t u
		$3\frac{3}{4}$	8.3.53	HR	10	2	N t u
			13.12.54				Died
J. C.	F	June 1948	27.3.53	h	20		N
		$7\frac{1}{4}$	4.1.56	h	5	5	N
B. C.	F	June 1953	29.6.53	H	8	6	N
		1	1.2.55	normal			A
			10.8.55				Rem
D. C.	M	June 1953	26.3.53	h	0	0	N
		3	3.5.55				Rem
A. D.	M	July 1950	26.5.53	R	0	0	N
		$6\frac{1}{4}$	9.5.55	normal	0	0	A
			31.12.55	H	0	0	A

(Table 1, cont.)

Patient	Sex	Date of onset & age at onset (yrs.)	Date	Urine			Clinical Condition
				Amino-acids	Glucose mg/100 ml	Fructose mg/100 ml	
C. D.	M	Sept. 1950	19.3.52	RR	500		N t u
		3¼	4.4.55	RRR	800		N u
M. G.	F	May 1953	17.6.53	normal	0	0	N t
		3½	9.2.55	normal			Rem
C. G.	M	Nov. 1951	17.11.52		60	15	N
		2¾	26.4.54				Died
A. G.	M	Apr. 1950	16.7.52	h			N
		4	8.10.52	H	5	2	N
			13.12.54	normal			A
			17.10.55				Rem
N. H.	M	May 1954	18.1.55	h	140	60	A
		5	13.5.55	normal	35		Rem
			15.11.55				Rem
E. H.	F	Born 11.4.52	27.2.53	normal	6	6	A t
		?	26.3.53	h	5		A
			10.4.53	H	10	25	N t
			19.4.53	H	25	8	N t
			7.5.53	h			N
			4.4.55	normal	8	8	A t
			23.7.55				A t
J. L.	M	May 1951	10.12.52	H	15	25	N t
		1¾	14.3.54				Died
G. L.	M	Feb. 1950	22.1.53	normal	5	7	A
		3	15.1.55				Rem
I. N.	M	July 1951	28.1.53	H	20	6	N u
		3	14.3.55	RRR	500	10	N u
			9.5.55	RRR			N u
			3.10.55				N u
E. O'B.	M	May 1952	16.7.52	H	60	12	N
		3	3.9.52	H	30	5	N u
			10.12.52	H	0	0	N
			7.1.53	h	7	6	N
			13.1.53	H	5	2	N
			8.4.53	HH	0	2	N
			3.6.53	H	50	5	N
			13.12.54	normal	0	8	Rem
			16.12.55				Rem
R. O'D.	M	Feb. 1953	25.2.53	h	5	0	N u
		¾	20.1.54				Rem

(Table 1, cont.)

Patient	Sex	Date of onset & age at onset (yrs.)	Date	Urine			Clinical Condition
				Amino-acids	Glucose mg/100 ml	Fructose mg/100 ml	
J. R.	F	July 1946	9.3.53	RR	700	0	N u
		$2\frac{1}{2}$	12.9.53				Died
I. S.	F	Aug. 1950	18.4.52	Rh	150	20	N t u
		$11\frac{3}{4}$	24.4.52	R	100	0	N u
			3.9.52	H	200	15	N t u
			4.10.52	Hr	100	6	Died
S. S.	F	Feb. 1954	15.11.54	Hr	45	4	N u
		$2\frac{1}{2}$	16.11.54	Hr			N u
			29.4.55				Died
S. U.	M	Feb. 1951	19.3.53	R	20		N t u
		$1\frac{3}{4}$	20.7.54				Died
J. T.	F	May 1954	19.8.55	H			N
		2	24.10.55				N
R. C.	M	May 1955	10.10.55	Hr	10	5	N
		$6\frac{1}{4}$					
P. M.	F	June 1955	11.10.55	Hr	10	4	N
		2	8.12.55	Rh	27	7	N u

h = slight
H = moderate
HH = very marked
} amino-aciduria of "H" pattern

r = slight
R = moderate
RR = very marked
RRR = gross
} amino-aciduria of "R" pattern

HR, Hr, Rh = patterns with components of both "H" and "R" in proportions indicated by the individual letters

u = azotaemia
N = active nephrosis
Rem. = remission
t = hypertension
A = albuminuria only

"R" and "H" patterns at different times; of these, 5 have died (6 months to 2 years after the "R" pattern was first observed), 4 still have manifest nephrosis and 2 have only albuminuria; the remaining patient in this group was observed for less than 6 months and is excluded from the analysis. The type of amino-aciduria appears therefore to bear some relation to the outcome of the disease. The occurrence of the "R" pattern has been associated with a graver prognosis; no child exhibiting this pattern has yet made a full recovery. As might be expected, the "R" pattern was found most commonly in those patients who had been ill for some time, and who showed other evidence of renal failure. Thus, of the 12 cases in this group, 8 had blood

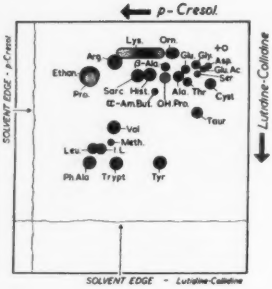


Fig. 4. "Map" of a paper chromatogram showing the position taken up by each amino-acid. (Reprinted by permission from the *Great Ormond Street Journal*, *1*, 76, 1951.)

Key

Alanine	= Ala.	Leucine	= Leu.
β-Alanine[1]	= β-Ala.	Lysine	= Lys.
α-Aminobutyric Acid	= α-Am.But.	Methionine	= Meth.
Arginine	= Arg.	Ornithine	= Orn.
Aspartic Acid	= Asp.	Phenylalanine	= Ph.Ala.
Cysteic Acid	= Cyst.	Proline	= Pro.
Ethanolamine	= Ethan.	Sarcosine[2]	= Sarc.
Glutamic Acid	= Glu.Ac.	Serine	= Ser.
Glutamine	= Glu.	Taurine	= Taur.
Glycine	= Gly.	Threonine	= Thr.
Histidine	= Hist.	Tryptophan	= Trypt.
Hydroxyproline	= OH.Pro.	Tyrosine	= Tyr.
Isoleucine	= I.L.	Valine	= Val.

[1] Citrulline takes up the same position on the chromatogram.
[2] β-Amino-isobutyric acid takes up the same position.

TABLE 2

Outcome of illness in relation to urinary amino-acid pattern.

Urinary amino-acid pattern	Number of cases	Outcome			
		Dead	Active nephrosis	Albuminuria only	Remission
Normal only	3				3
"H" only	11	2	1	2	6
"R" only	3	2	1		
"R" and "H"	7	2	3	2	
HR	1	1			

ureas over 40 mg per 100 ml and 5 had definite and 1 border-line hypertension; only 2 had neither azotaemia nor hypertension, and only 3 had been ill for less than 18 months. Of the 2 cases with the "R" pattern but without other evidence of renal failure, 1 has residual albuminuria only and 1 has active nephrosis. Of the 8 patients showing both patterns at different times, 5 had the "H" pattern before the "R" pattern and 3 reverted to the "H" pattern after the "R" pattern.

Glucose, in concentrations of 20 to 800 mg per 100 ml, was found in 31 specimens of urine from 16 patients, and fructose in concentrations of 10 to 60 mg per 100 ml in 14 specimens from 12 patients. The remaining 29 specimens were within the normal range of sugar content. Glycosuria was found in 10 out of the 11 cases showing the "R" pattern of amino-aciduria.

The amount of glucose in the urine tended to parallel the degree of amino-aciduria and the severity of the disease. Of the 16 patients in whom it was observed, 6 died, 6 still have active nephrosis, 2 have albuminuria and 2 have recovered.

Seven samples of blood from 5 patients were examined for amino-acids. β-Amino-isobutyric acid was present in marked excess over the normal in one specimen from E. O'B (but was normal in 2 other specimens), and was slightly increased in specimens from S. S., I. S., E. B., J. L. Traces of ethanolamine, not normally demonstrable in the quantities of plasma used, were present in specimens from E. O'B., I. S., E. B., and J. L. All other amino-acids were within the normal range.

Discussion

For several reasons, we feel it is unlikely that the amino-aciduria observed in the nephrotic syndrome is an artefact caused by breakdown of the protein present. First, no active proteases have been reported to be present in nephrotic urines, and the urines have been kept under conditions likely to inhibit their action if present. Trichloracetic acid or sulphonated polystyrene resin could not cause any appreciable hydrolysis of protein in the short time they are in contact, particularly as they are not heated together. Moreover, no difference can be detected by paper chromatography between the amounts of amino-acids in normal serum whether deproteinised by trichloracetic acid or by ultrafiltration (Woolf, unpublished data). Secondly, although amino-aciduria is almost invariably found in the presence of proteinuria (and this is to be expected, since proteinuria is practically never absent if the disease is active) amino-aciduria has been observed in the absence of albuminuria in one of the cases on one occasion. Thirdly, taurine, ethanolamine and β-amino-isobutyric acid, which are frequently found in nephrotic urines, are not breakdown products of plasma protein. We believe, therefore, that there is a true amino-aciduria in the nephrotic syndrome. A number of these patients were receiving high protein diets at the time of investigation. Amino-aciduria was, however, observed on several occasions in subjects not receiving a high protein intake; and an increased protein intake does not in normal individuals cause amino-aciduria of the degree seen in nephrosis (Eckhardt and Davidson; Woolf, unpublished data).

Whether the amino-aciduria is the result of a failure of renal tubular reabsorption or of an abnormal blood amino-acid pattern reflecting a disturbance in amino-acid metabolism is uncertain. As already described, urinary amino-acid patterns compatible with either explanation have been observed, sometimes indeed in the same patient at different times. However, since the

"R" pattern has been observed in many conditions in which the renal tubules do not reabsorb amino-acids efficiently, and in the present series was found predominantly in those cases suspected on other grounds of having irreversible renal damage, it seems likely to be of renal origin. This view is supported by the occurrence of glycosuria in the same type of case. Hawkins *et al.* investigated a group of patients with renal disorders and found glycosuria in many of those with chronic nephritis and in all of the nephrotics. Many of their cases also had impaired glucose tolerance, but glycosuria occurred when blood sugar levels were below the usual renal threshold and was found even when the subjects were fasting. It seems likely, therefore, that glycosuria in the nephrotic syndrome is due to a defect of renal tubular reabsorption.

Interpretation of the findings in cases with the "H" pattern of amino-aciduria is more difficult. These patients have shown a greater tendency to recover, and their amino-aciduria has not been associated with other evidence of renal failure nor, in most cases, with glycosuria. The increased amounts of α-amino-acids excreted by these cases do not seem to be due to raised blood amino-acid levels since these were within normal limits in the five specimens examined from 3 such patients. Furthermore, Farr and MacFadyen found a persistent slight reduction in plasma α-amino-acid nitrogen, which was strikingly accentuated during "nephrotic crises", in children with the nephrotic syndrome. Shreeve *et al.* in 2 adults and Plückthun *et al.* in children also found a general tendency towards low plasma α-amino-acid levels. The position is somewhat different in the case of the other amino-compounds (ethanolamine, β-amino-isobutyric acid and taurine) that compose the urinary "H" pattern. β-Amino-isobutyric acid was present in increased amounts in 3 of the 5 specimens of blood, and ethanolamine was probably increased in two of them. Since the plasma samples were treated by the ion-exchange resin technique, taurine would not have been detected. These three compounds are also found in the urine in increased amounts in some cases of hepatic dysfunction. There is some independent evidence of hepatic dysfunction in the nephrotic syndrome. Aubry *et al.* observed fatty and, in one case, cirrhotic changes in the livers of 2 out of 4 cases of lipoid nephrosis. Flood and Pinelli and Portier *et al.* demonstrated a reduced ability to methylate glycocyamine in nephrosis. Gottfried *et al.* found evidence of slight hepatic dysfunction in all of ten nephrotic children. Gitlin *et al.* using radioactive tracer techniques, showed a great increase in the rate of catabolism of plasma proteins in nephrotics and concluded that their metabolism was markedly disturbed.

It is tentatively suggested that the "H" type of amino-aciduria is due to two distinct causes: a renal tubular leak responsible for the appearance

of leucine, valine and (probably) tryosine, but of smaller magnitude than that occurring in patients showing the "R" pattern; and a disturbance of metabolism causing the appearance of ethanolamine, β-amino-isobutyric acid, and sometimes taurine. The wide variation between the relative amounts of these two groups of amino-compounds present in the urine supports such a duality of mechanism.

Summary

The urines of 29 children with the nephrotic syndrome were investigated for amino-acids and sugars by paper chromatography. Amino-aciduria was found in 25 patients and glycosuria in 16 patients.

Amino-aciduria occurred predominantly in two patterns, one strongly suggesting a defect in renal tubular reabsorption, the other possibly reflecting a disturbance in amino-acid metabolism associated with a lesser defect in tubular reabsorption; the prognosis was worse for children showing the first pattern.

Étude chromatographique des acides aminés et des sucres au cours du syndrome néphrotique.

L'élimination urinaire des aminoacides et des sucres a été étudiée chez 29 enfants néphrotiques par chromatographie sur papier. Une aminoacidurie était trouvée chez 25 males, et une glycosurie était notée 16 fois. L'aminoacidurie survenait principalement chez deux malades. L'un de ces cas présentait un trouble du métabolisme des acides aminés associé à un degré minime de la réabsorption tubulaire. Le pronostic semblait plus mauvais dans les cas dont l'aspect paraissait traduire un déficit de la réabsorption tubulaire.

Ausscheidung von Aminosäuren und Zucker im Urin bei Nephrose-Syndrom. Eine chromatographische Studie.

Der Urin von 29 Kindern mit nephrotischem Syndrom ist durch Chromatographie auf Aminosäuren und Zucker untersucht worden. Bei 25 Patienten wurde Aminoacidurie und bei 16 Patienten Glykosurie gefunden. Aminoacidurie kam vorherrschend bei zwei Patienten vor, von denen einer eine deutliche Störung im Aminosäurestoffwechsel, verbunden mit einem geringeren Schaden der tubulären Rückresorption zeigte; bei den anderen kann möglicherweise ein Schaden der tubulären Rückresorption angenommen werden. Die Prognose war schlechter für die Kinder, die den ersten Befund zeigten.

Excreción urinaria de aminoácidos y azúcares en el sindrome nefrótico. Estudio cromatográfico.

Se estudió la orina de 29 pacientes afectos de sindrome nefrótico por medio de la cromatografía en papel. En 25 de ellos se encontró aminoaciduria y en 16 glucosuria. La aminoaciduria apareció predominantemente en dos pacientes, en uno de ellos reflejando un disturbio del metabolismo aminoácido asociado con ligero defecto de la reabsorción tubular. El pronóstico fué peor en los niños que presentaron el primer cuadro, sugiriendo la segunda probabilidad un defecto de la reabsorción tubular.

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Experimental Approach to the Pathogenesis of Retrolental Fibroplasia

VIII. The Production of Irreversible, Severe Eye Changes through Intense and Prolonged Oxygen Exposure in Mice

by BO E. HELLSTRÖM

Introduction

The similarity between the microscopic changes of the retina in oxygen-exposed animals and the early pathologic findings in retrolental fibroplasia is striking (Patz *et al.* (11, 12), Ashton *et al.* (1), Gyllensten and Hellström (4, 5)). As for the progression and the final stages of the respective diseases, however, the patterns are divergent. Almost without exception the experimental lesions, so far described, have been more benign and reversible in their course, whereas the disease in premature children frequently progresses to a cicatricial stage with the detached retina taking part in the formation of a retrolental membrane.

In the experiments reported by Patz (11), where newborn animals of different species were exposed to oxygen, the only more advanced and persistent pathologic finding described was a detachment of the retina in two of the twenty puppies studied. Extensive hemorrhage into the vitreous preceded the retinal detachment.

In the animal studies presented by Ashton *et al.* (1), dealing mainly with oxygen-exposed kittens, the long-term results of the oxygen-induced vaso-obliteration consisted of revascularization, where the general architecture differed considerably from the normal. The histological picture of the retina, however, was restored to normal, apart from acute-angled folds in the posterior half of the eye. There was no evidence of retinal detachment.

Gerschman *et al.* succeeded in producing atrophic lesions of the retina in the eyes of newborn mice by continuous exposure to 70 per cent oxygen.

This study was aided by grants from the Swedish National Medical Research Council.
The gas mixture was generously supplied by Svenska Aktiebolaget Gasaccumulator (AGA), Stockholm-Lidingö, Sweden.

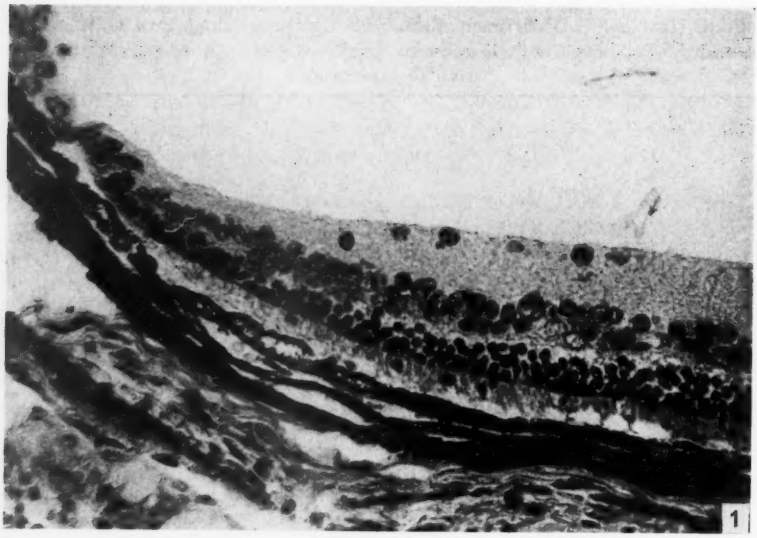


Fig. 1. 6-month-old mouse kept in oxygen the first 5 days of life. Moderate atrophy of all layers in the periphery of the retina. Compare with Fig. 2. (× 420)

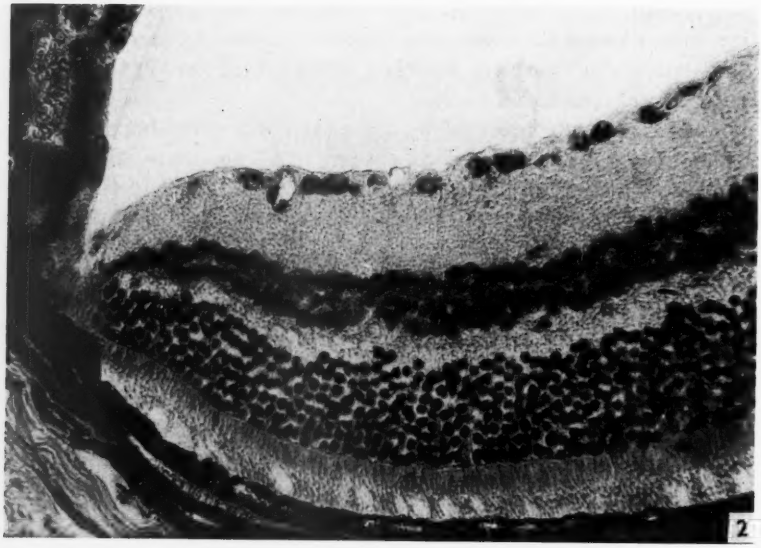


Fig. 2. 6-month-old control animal. Normal retina. (× 420)

The atrophy included loss of ganglion cells and inner nuclear layer, and spotty distortion of the outer nuclear layer.

In previous experiments irreversible damage of the retina has been reported as following oxygen exposure of young mice. The chief characteristics were atrophic changes, especially of the inner layers, with a reduced number of ganglion cells, reduction of the inner plexiform and the inner nuclear layers and fusion of the nuclear layers. These changes were described as having followed both concentrated oxygen exposure (4, 5) and the use of oxygen at lower concentrations (7). On using concentrated oxygen during an exposure of only 5 days, atrophies which occurred especially in the periphery of the retina have now been observed to still persist after half a year (6) (Figs. 1 and 2).

The purpose of the present investigation was to explore the maximal injurious effect of oxygen on the eyes of newborn mice. It was thought especially of interest to find out if a cicatricial stage, similar to that found in retrolental fibroplasia, could be produced. Prolonged exposure to concentrated oxygen was used. In order to allow proliferative changes of the retinal vessels to occur, the oxygen exposure was interrupted at regular intervals, the exposure thus being performed in an intermittent way.

Material and Methods

The strain of black mice, the feeding and handling of the animals, the type of gas chambers, the flow of oxygen, and the method for checking its concentration were the same as used in previous experiments (4, 5). CO_2 was not measured, the temperature varied between 20 and 25°C. The oxygen concentration ranged between 98 and 100 per cent. Replacement of the oxygen with air or the air with concentrated oxygen during the intermittent exposure, took place within a few minutes. The duration of oxygen periods and the interval between these varied. In most experiments three days of oxygen exposure were followed by a three days' stay in air and this was repeated for 1–3 months. In another smaller group this interchange took place every day for two months followed by one month continuously in air. In a third group the recurrent oxygen period was five days and the interval in air 10 days for 1–1½ months. The mothers were interchanged every second day in all groups with those from control litters.

The eyes of 44 animals, all newborn at the beginning of the oxygen exposure, were prepared and examined, and the same histological technique as described previously (4, 5) was used.

Results

The prolonged, intermittent oxygen exposure resulted in changes of the eyes, sometimes of an intensity not previously observed. They were mainly located to the retina, where the most constant and conspicuous finding was an atrophy of different retinal layers. In cases with moderate changes only

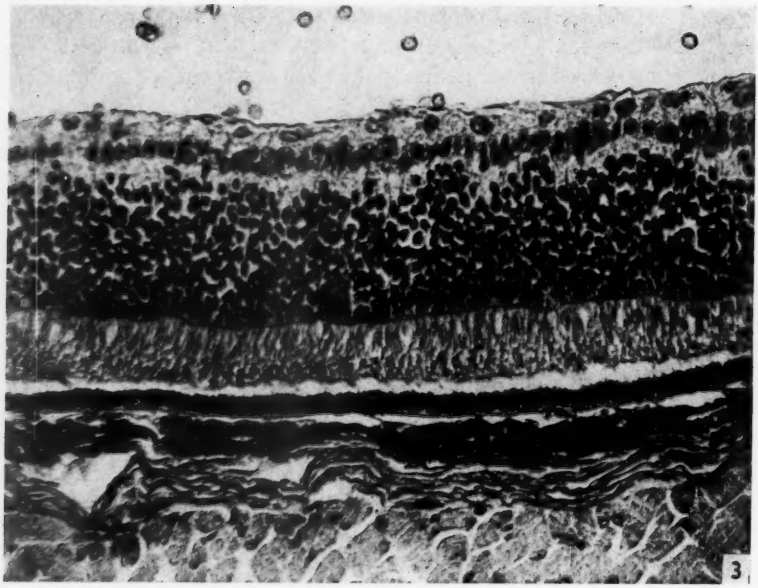
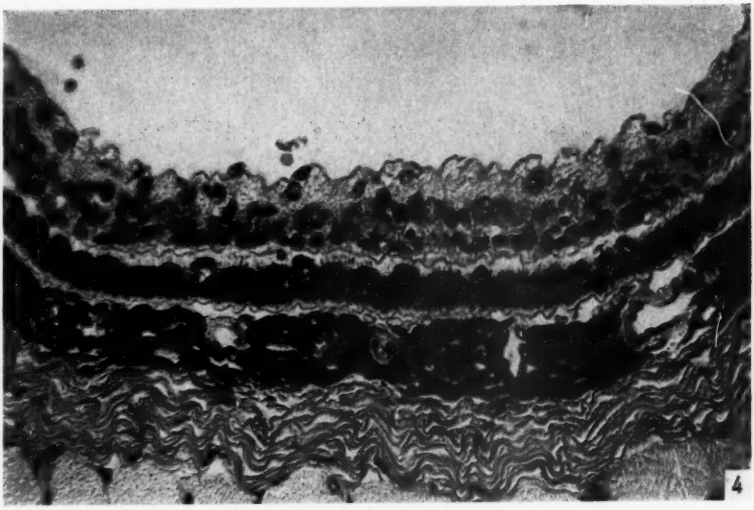


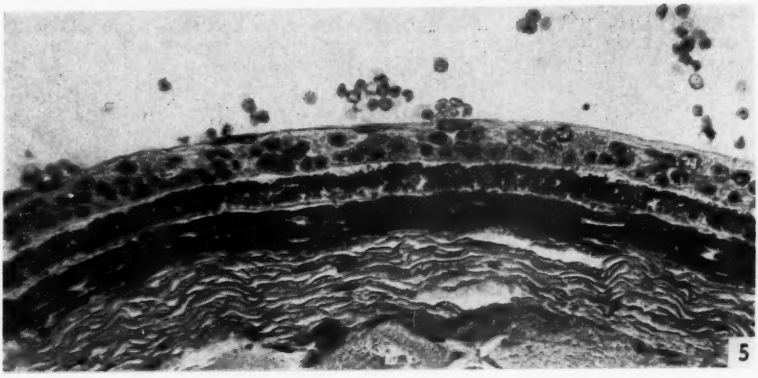
Fig. 3. 1-month-old animal intermittently kept in oxygen since birth. Moderate atrophy of the inner layers of the retina. Hemorrhage in the vitreous body. (× 420)

the inner, vitreal layers were affected. The ganglion cells were few, the inner plexiform layer thin, the inner nuclear layer reduced to one or a few rows of cells, often fused with the outer nuclear cells (Fig. 3). In more advanced atrophies the inner layers had entirely disappeared and the outer nuclear layer was lying directly towards the vitreous body. In the most severe cases the atrophy included visual cells with rods and the retina consisted of a few rows of intermixed cells built up by scattered remnants from the retinal layers (Figs. 4 and 5). In one case a discontinuance of the retina with ingrowing connective tissue elements was demonstrated (Fig. 6).

The whole of the retina of one eye was usually not affected to the same degree in all parts. The most severe changes were commonly located in the midperiphery, whereas the periphery near ora serrata was better preserved. This was true also of the part closest to the papilla, but here on the other hand irregularities of layers, fusion and folds were frequently encountered.

The occurrence of true detachments is sometimes difficult to determine as similar pictures can be produced by shrinking and artefacts. One type of shallow detachment occurred occasionally, however, in connection with





Figs. 4 and 5. 2-month-old animal intermittently kept in oxygen since birth. Severe atrophy of all layers of the retina with only a few rows of intermixed cells persisting. Hemorrhage in the vitreous body. (× 420)

severe atrophic changes of the retina, where such a technical error could not be responsible. In these cases the space between the detached retina and pigment epithelium was partly invaded by large, sometimes multinuclear cells, some of them containing pigment and were most likely derived from the pigment epithelium (Fig. 7). This proves that the separation can-

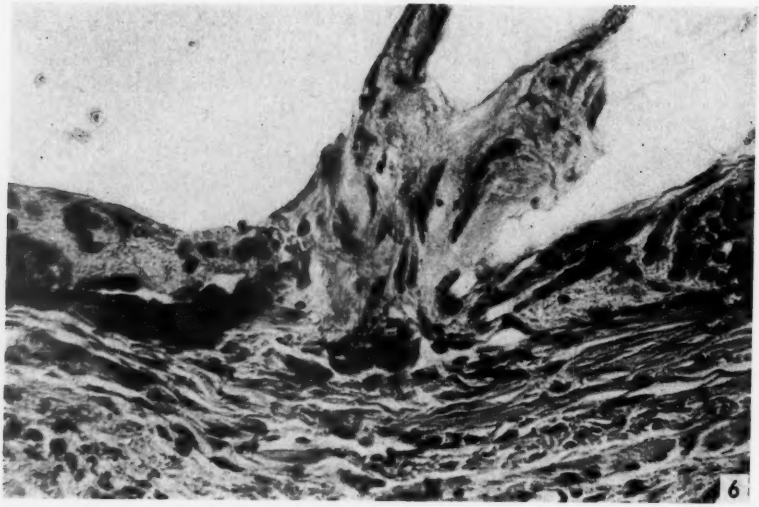


Fig. 6. 2-month-old animal intermittently kept in oxygen since birth. Severe atrophy of all layers of the retina with discontinuance and ingrowth of connective tissue from the choroid. (× 420)

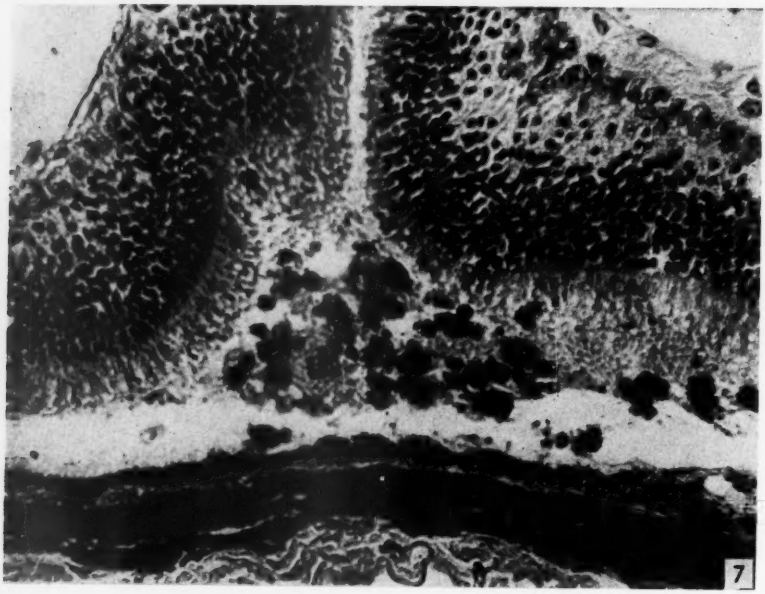


Fig. 7. 3-month-old animal intermittently kept in oxygen for the first two months. Detachment of the atrophic retina. Proliferating pigment epithelium forming a cluster. (× 420)

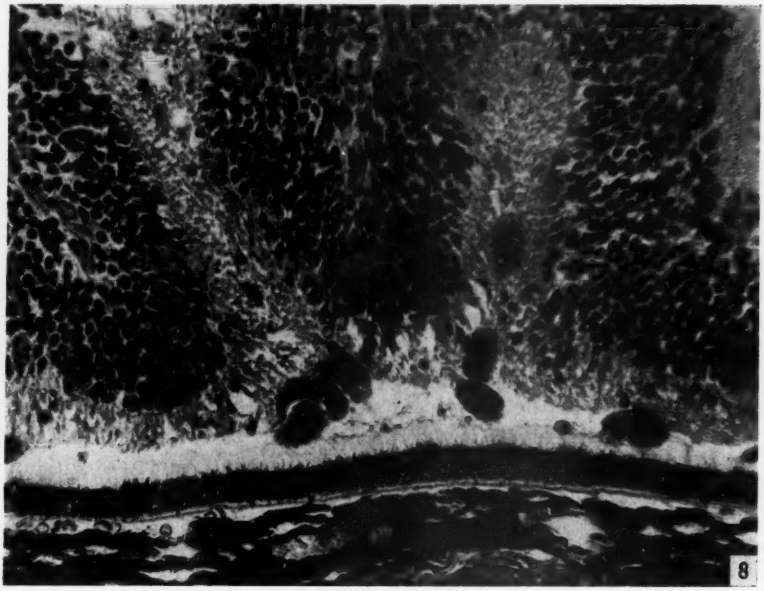


Fig. 8. 1-month-old animal intermittently kept in oxygen from birth. Folding of the retina with pigment cells in the subretinal space. (× 420)

not be purely an artefact. Similar pigment cells were sometimes found in the space between the pigment epithelium and the sharp-angled folds in the centre of the retina (Fig. 8).

A more extensive or total detachment of the retina did not occur in any case.

The vascular proliferations, characteristic of the early changes of the oxygen-induced changes of the eyes in young mice were still present one month following the onset of exposure, both as budding of the vessels in the nerve fibre layer and as proliferative hyaloid vessels with hemorrhages in the vitreous body. At two months of age the retinal vascular hyperplasia had disappeared leaving a nerve fibre layer irregularly and incompletely vascularized. The hyaloid vessels still persisted at this age, but at three months they were no longer found.

Fibrillary structures, stained as collagen, and mononuclear cells were sometimes surrounding and traversing the vitreous hemorrhages, but no real organization had taken place.

The more severe and intense changes now described were most frequently

seen among cases, where the duration of each oxygen-period had been three days. In the animals, where the same periods were five days, the atrophic changes were only slight, though regularly found.

Discussion

The new information to be gained from the present study is that an injury of the retina, of a severity not previously observed, can be induced by a prolonged intermittent exposure to oxygen. The main feature is an atrophy and the mechanism is probably based on the impaired vascularization due to the oxygen effect. In these experiments the atrophy has reached a subtotal stage, where all the retinal layers are severely affected. Shallow retinal detachments have also been demonstrated. These might be due to a failure of growth of the atrophic retina as compared with the pigment epithelium and outer layers of the eye, which has been suggested to be the mechanism for similar detachments in microphthalmic human eyes (Mann).

The occurrence of abnormal pigmented cells in the space between the atrophic layers and the pigment epithelium has not been described previously in the oxygen-induced disease of the animal eye. Similar pictures have been shown, however, after experimental injury of visual cells in the rabbit by injection of mono-iodoacetate (Karli).

In spite of the excessive oxygen trauma used in the present investigations, the picture of a final cicatricial stage of retrolental fibroplasia with complete detachment and membrane formation was not produced.

Different hypotheses can be offered to explain this discordance. The lens in mice is relatively large and might support the retina in its normal position as suggested by Patz (11). Another essential point seems to be the relative paucity of connective tissue elements following the capillary proliferations in the mouse eye as compared with those seen in eyes with advanced stages of retrolental fibroplasia. The shrinking of these fibrous elements is generally accepted as the main cause for the retinal detachment. Whether the less tendency to fibrous organization in the animal eye is due to primary differences in structure and mode of reaction compared with the infants' eye, or if other environmental factors are in action in retrolental fibroplasia is impossible to decide at present. Our knowledge of the processes leading to retinal detachment in retrolental fibroplasia is too incomplete. This is illustrated by cases described as retrolental fibroplasia, where a complete detachment has occurred, before any ingrowth of pathologic vessels or connective tissue in the vitreous body is evident (Krause).

Recent animal work by Ashton and Cook (2) has also shown that a *primary* detachment of the developing kitten retina can lead to a *secondary* prolifera-

tion of retinal vessels to form glomerular tufts in the vitreous body without any oxygen exposure.

In spite of the lack of complete conformity between the oxygen-induced changes of the mouse eye and retrolental fibroplasia this study has shown that intense and prolonged oxygen exposure might lead to a severe retinal damage of the animal eye, without doubt seriously impairing its function.

Summary

1) The effect of an intense and prolonged intermittent oxygen exposure on the immature mouse eye was studied.

2) The exposure resulted in apparently irreversible eye changes, mainly as an atrophy of the retina of varying degrees. The most intense atrophies included all layers, reducing the retina to a few rows of intermixed cells. This severely injured retina must also signify a seriously impaired function.

3) In a few cases shallow detachments occurred with signs of proliferating pigment epithelium but no complete detachment was observed.

4) The differences between the oxygen-induced disease of the mouse eye and retrolental fibroplasia, concerning their respective final stages are discussed.

Contribution expérimentale à la pathogénie de la fibroplasie rétrolentale. VIII. La production de lésions oculaires graves et irréversibles par exposition prolongée de souris en atmosphère suroxygénée.

L'effet sur l'œil de souris immature d'une exposition prolongée en milieu suroxygéné a été étudié. De l'exposition résultent des lésions oculaires apparemment irréversibles, et principalement une atrophie de la rétine à des degrés variables. Les atrophies les plus intenses atteignaient toutes les couches cellulaires de la rétine, réduisant celle-ci à quelques épaisseurs de cellules mélangées. A une atteinte aussi sévère de la rétine correspond certainement une altération fonctionnelle grave. Dans un petit nombre de cas, on observait des soulèvements des couches cellulaires superficielles et des signes de prolifération de l'épithélium pigmenté, mais en aucun cas on ne pouvait noter de soulèvement global. Les différences entre les lésions provoquées par l'oxygène sur l'œil de la souris et la fibroplasie rétrolentale du prématuré, ainsi que leur devenir ultérieur, sont discutés.

Experimenteller Beitrag zur Pathogenese der retrolentalen Fibroplasie. VIII. Die Erzeugung von irreversiblen, schweren Augenveränderungen durch intensive und anhaltende Sauerstoffeinwirkung bei Mäusen.

Die Wirkung einer intensiven und verlängerten intermittierenden Sauerstoffeinwirkung auf das unreife Mäuseauge ist untersucht worden. Die Einwirkung ergab anscheinend irreversible Augenveränderungen, hauptsächlich als Atrophie verschiedenen Grades der Retina. Die stärksten Atrophien umfassen alle Schichten und reduzierten die Retina bis auf wenige Reihen gemischter Zellen. Diese schwer geschädigte Retina muss auch eine ernstlich beeinträchtigte Funktion bedeuten. In einzelnen Fällen kam oberflächliche Ablösung mit Zeichen von Proliferation des Pigment-

epithels vor, aber es wurde keine vollständige Ablösung beobachtet. Die Unterschiede zwischen der sauerstoffinduzierten Erkrankung des Mäuseauges und der retrolentalen Fibroplasie hinsichtlich ihrer jeweiligen Endstadien werden diskutiert.

Intento experimental de aclarar la patogénesis de la fibroplasia retrolental. VIII. La producción de severos e irreversibles cambios oculares mediante la intensa y prolongada exposición de ratas a oxígeno.

Se estudiaron los efectos de una exposición intermitente, intensa y prolongada de ratas inmaduras a O_2. De dicha exposición resultaron cambios en el ojo, aparentemente irreversibles, sobre todo atrofia de retina de grados variables. Las atrofias mas pronunciadas incluyeron todas las capas, reduciendo la retina a solo algunas filas de células mixtas. Esta retina seriamente dañada debe acarrear también una función severamente disminuída. En unos pocos casos ocurrieron desprendimientos pequeños con proliferación de un epitelio pigmentado. No se observó desprendimiento total. Se discute la diferencia entre los cambios producidos por oxígeno en los ojos de rata y la fibroplasia retrolental, considerando sus respectivos estadios finales.

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From the Maternity Clinic, Sabbatsberg Hospital, Stockholm (Head: Prof. PER WETTERDAL, M.D.)

Influence of Synthetic Vitamin K on Capillary Resistance of the Newborn

by BJÖRN WESTIN

Introduction

Hypoprothrombinemia in normal newborns was first described by Brinkhous, Smith & Waerner (1937). According to Dyggve, the prothrombin values were found to fall rapidly from 12 hours after birth. The effect of different vitamin K preparations on prothrombin time was studied by Larsen, who found that the effect set in after a few hours and reached a maximum after about 18 hours. Vitamin K administered to the newborn shortly after birth may therefore safely be used in eliminating hypoprothrombinemia. The same results may be obtained by administering vitamin K to the mother. This was first shown by Hellman & Shettles, Larsen & Plum, and its value has later on been stressed by Dyggve in his dissertation. He found that the incidence of intracranial bleeding without evidence of tentorial rupture, suprarenal hemorrhages, hematemesis and melena neonatorum was significantly suppressed when synthetic vitamin K was administered to the mother. On the other hand the incidence of chephalohematomas, intracranial bleeding combined with tentorial rupture and cutaneous hemorrhages was not significantly altered. In these cases birth trauma may play an important role. In this connection Dyggve pointed out the possibility that synthetic vitamin K administered to the mother in large doses during a long time might also increase capillary resistance of the newborn.

The purpose of the present investigation was to find out if prophylactic administration of synthetic vitamin K in adequate doses to both mother and child instead of only to the newborn could significantly suppress the incidence of hemorrhages in the newborn. If this was the case, it seemed possible that synthetic vitamin K might increase capillary resistance of the newborn.

Material and Method

The material was obtained from consecutive deliveries at the Maternity Clinic, Sabbatsberg Hospital, Stockholm, in the years 1949–1955. The obstetric and pediatric care as well as the diagnostic recording were uniform and unchanged during the period.

Premature newborns shorter than 35 cm and those who did not breathe were not included in this material.

The same preparation of synthetic vitamin K (2-methyl-1,4-naphtylen tetranatr diphosph.) was used in every instance. In the years 1949–1952, 5 mg vitamin K were administered intramusculary to 5817 newborn infants shortly after birth (control group). During the following years, 20 mg vitamin K were administered orally to the mothers on admission to the delivery department, and in addition 5 mg were given intramusculary to the newborns ("protective" group) as in the control group. The "protective" group comprised 7201 newborn infants.

Results

In order to get an idea of the accuracy of the results, it seemed necessary to compare the two groups of hemorrhages with regard to stress factors during labour. Table 1 indicates that the incidence of occiput presentations, breech presentations and forceps deliveries was approximately the same in the two groups. As indicated in Table 2, the time interval between orally administered vitamin K and delivery was satisfactory in the majority of the hemorrhagic cases.

TABLE 1

Incidence of different types of deliveries in control and "protective" group.

Group	Normal delivery in Occiput presentation	Breech delivery	Forceps delivery	Cesarean section
Control	37	6	15	1
"Protective"	54	6	21	1

TABLE 2

Time interval between the oral administration of vitamin K to the mother and the delivery of infants with hemorrhagic diseases in the "protective" group.

Hours before delivery	Number of infants
0– 1	0
1– 2	5
2– 4	8
4–12	27
12–24	17
24–48	13
48–	12
Total number	82

TABLE 3

Incidence of hemorrhages in prematures.

Group	Total number of prematures	Hemorrhages in prematures
Control	239 (4.1 %)	6 (1.0±0.4‰)
"Protective"	306 (4.2 %)	14 (1.9±0.5‰)

TABLE 4

Total number of hemorrhages in control and "protective" group.

Group	Total number of hemorrhages
Control	1.01±0.13 %
"Protective" . . .	1.13±0.12 %
Difference	0.12±0.14 %

TABLE 5

Incidence of hemorrhages in the newborn.

Hemorrhages in the newborn	Control	"Protective"
Intracranial hemorrhages without evidence of tentorium rupture	20	28
Hematemesis	0	2
Melena neonatorum	4	4
Subcapsular hemorrhages of the liver	1	0
Suprarenal hemorrhages	0	2
Total number of cases	25 (4.3±0.9‰)	36 (4.9±0.8‰)

TABLE 6

Incidence of hemorrhages in the newborn.

Hemorrhages in the newborn	Control	"Protective"
Cephalohematoma	10	20
Intracranial hemorrhages combined with tentorium rupture	21	24
Cutaneous hemorrhages	3	2
Total number of cases	34 (5.8±1.0 ‰)	46 (6.4±0.9 ‰)

The incidence of prematures was approximately the same in both groups and there was no significant difference in the incidence of hemorrhages (Table 3).

The total number of hemorrhages in the material is indicated in Table 4. There was no significant difference between control and "protective" group. Each group was divided into two subgroups. In one of these groups, intracranial hemorrhages without evidence of tentorium rupture, hematemesis, melena neonatorum, subcapsular hemorrhages of the liver and suprarenal hemorrhages were collected (Table 5). There was no significant difference between control and "protective" group.

The second subgroup comprised cephalohematoma, intracranial hemorrhages combined with tentorium rupture and various cutaneous haemorrhages (Table 6). There was no significant difference between control and "protective" group.

Summary and Conclusions

1. Synthetic vitamin K was administered to 5817 newborn infants and in 7201 cases to both mother and newborn.

2. There was no significant difference in the incidence of hemorrhages between the two groups. It seems sufficient to administer vitamin K only to the newborn.

3. It may be concluded that in the doses given, synthetic vitamin K administered to the mother did not seem to increase capillary resistance of the newborn infant.

Influence de la vitamine K synthétique sur la résistance capillaire du nouveau-né.

De la vitamine K synthétique a été administrée à 5.817 nouveaux-nés, et dans 7.201 cas à la fois à la mère et à l'enfant. On n'a pas noté de différences appréciables dans la survenue des hémorragies par comparaison des deux groupes. Il semble donc suffisant d'administrer seulement de la vitamine K à l'enfant. On peut conclure par conséquent qu'aux doses données, la vitamine K synthétique administrée à la mère ne semble pas accroitre la résistance capillaire du noveau-né.

Der Einfluss von synthetischem Vitamin K auf die Kapillarresistenz bei Neugeborenen.

Synthetisches Vitamin K wurde 5817 Neugeborenen und in 7201 Fällen sowohl Mutter wie Neugeborenem verabreicht. Es bestand kein deutlicher Unterschied im Vorkommen von Blutungen zwischen den beiden Gruppen. Es scheint ausreichend zu sein, Vitamin K lediglich den Neugeborenen zu verabfolgen. Es kann angenommen werden, dass die der Mutter verabreichte Dosis von synthetischem Vitamin K nicht die Kapillarresistenz des Neugeborenen erhöht.

Influencia de la vitamina K sintética sobre la resistencia capilar del recién nacido.

En 5817 casos se administró vitamina K sintética a recién nacidos y en 7201 a ambos madre e hijo. No hubo diferencia significativa en la incidencia de hemorragias en ambos grupos. Parece suficiente administrar vitamina K solo al recién nacido. Puede ser concluído que, en las dosis empleadas, la vitamina K sintética administrada a la madre no parece aumentar la resistencia capilar del recién nacido.

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Tetracycline Treatment of Whooping-Cough

by HANS JERNELIUS

Of recent years the literature has contained many reports on the effect of so-called broad-spectrum antibiotics in cases of whooping-cough. The antibiotics studied in the first place are chloramphenicol (chloromycetin), chlortetracycline (aureomycin), and oxytetracycline (terramycin). The major proportion of workers reported encouraging results, but many studies had been carried out without control series.

Hedlund & Mossberg treated 72 cases with chloramphenicol. The same number, being given a placebo, served as controls. In infants, the effect seemed to be beneficial both in the catarrhal and paroxysmal stages. In children older than 1 year, the effect was satisfactory if treatment was started in the catarrhal stage, whereas treatment started in the paroxysmal stage was entirely futile. The action of the drug was assessed by determining the decrease in paroxysms during and after treatment as compared with the controls. This decrease was significant statistically. Following treatment, all patients who had been given chloramphenicol were free of *Haemophilus pertussis*. Here also the difference between treated and control cases was significant statistically.

Claesson & Lindquist used chloramphenicol in a series including 83 children. Half the series in addition received penicillin or streptomycin conjointly with chloramphenicol. There were no controls. The result of treatment was considered satisfactory when the drug had been instituted during the first week of illness. No difference emerged between the group treated exclusively with chloramphenicol and that receiving combined treatment.

In England, an extremely careful investigation was performed by the British Medical Research Council (3). Three groups comprising 100 cases each were treated, one receiving chloramphenicol, one chlortetracycline, and one a placebo. No difference in effect was demonstrable between chloramphenicol and chlortetracycline. When all the cases were assessed together, the action was considered negligible. In those instances where treatment had been started within the first eight days of illness, the result was satisfactory. In these cases the course was milder, with fewer and less severe paroxysms than in the controls. However, the effect was not dramatic. The treated cases attained freedom from *H. pertussis* earlier than did the controls, i.e. computed for the entire material. The complications were evenly distributed among the three groups. Three cases, viz. one in each group, were fatal.

de Rudder & Vetterman reported on a group of 383 infants treated with chloramphenicol or chlortetracycline during the 5-year period 1948–1953. These were compared with 318 untreated cases during the 10-year period 1937–1947. It was found that (a)

the period of hospitalization decreased from 11 to 4½ weeks; (b) the death-rate declined from 17.5 % to 3.9 %; and (c) the rate of pneumonia in the untreated group was 23.6 % versus 4.8 % in the treated group.

Likewise, oxytetracycline has proved satisfactory in many quarters (Zischinsky, Newman *et al.*, and others).

Since tetracycline had been released in November, 1953, it has been tried in a large number of different infections. It is stated to have the same antibacterial spectrum as chlortetracycline and oxytetracycline, *in vitro* inhibiting the growth of *H. pertussis*. The incidence of gastroenteric side-effects is said to be considerably lower than in the cases of chlortetracycline and oxytetracycline (9, 10, 11).

As regards the use of tetracycline in pertussis, we have been able to find but one study in the literature. Wood, Dowling and their associates reported on 184 cases of various infections, among them 26 cases of whooping-cough, treated with tetracycline. No more detailed statements are made concerning the material, and there is no control series. However, in 24 of the 26 treated cases of pertussis the response to treatment was termed satisfactory, the effect being equal to that previously observed with chlortetracycline. Complications supervened in 2 cases only, viz. pneumonia and cystitis in one, and morbilli with a fatal outcome five days after the eruption, in the other.

Materials and Methods

In the Hospital for Contagious Diseases in Stockholm we have treated 54 cases with tetracycline, Tetracyn (Pfizer and Kabi) being used. This was given as coated tablets of 50 mg each. Forty-two cases served as controls and received a placebo, viz. coated tablets of precisely the same taste and appearance as the drug proper.

Irrespective of sex, age, and stage of illness every other case was given the placebo and every other Tetracyn. The tablets were marked with different letters, and neither the nursing-staff nor the medical observers were aware of which kind of tablets contained the drug.

Initially the series consisted of 130 cases, half of which were controls. Of these, the following were subsequently excluded: 3 owing to doubtful diagnosis, 4 where the course of treatment was less than 4 days, 5 having received chloramphenicol prior to admission or having been given immune-globulin early in the catarrhal stage, 1 with incomplete record, and 21 where symptoms had been present for more than 4 weeks when the treatment was started.

Of the 54 treated 13 were infants of whom 8 were below the age of 6 months, 19 were aged 1–3 years, 13 3–5 years, and 9 were older than 5 years. Of the 42 controls 7 were infants, 16 aged 1–3 years, 11 3–5 years, and 8 older than 5 years.

The dosage was 30 mg/kg body weight daily, divided into 4 doses. The first dose was given at 8 a.m., the last at 8 p.m. The treatment was continued for 7 days. The children were first observed for 4 days following admission,

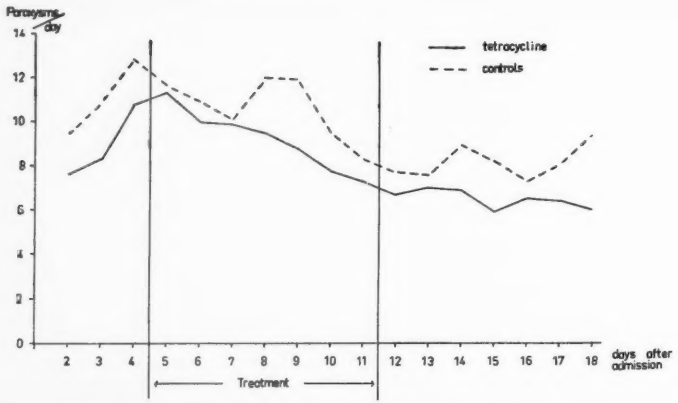

Fig. 1. Catarrhal and paroxysmal pertussis with less than a fortnight's symptoms prior to admission (13 and 25 cases respectively).
Treated: 23 cases with cough on an average 9.6 days prior to admission
Controls: 15 „ „ „ „ „ „ 9.3 „ „ „ „

the treatment being instituted in the morning of the 5th day. At the first signs of diarrhoea the drug was instantly withdrawn. Pernasal swabs and cough plates for the isolation of *H. pertussis* were taken daily during the first 4 days, then on the 3rd day of treatment, and subsequently at weekly intervals.

The effect of the treatment was assessed by the number of paroxysms and "whoops". The children were referred to a special pertussis ward, and the paroxysms were recorded day after day by trained personnel perfectly familiar with this particular type of nursing.

The material was divided into two groups. In Group 1 are included cases where the symptoms had been present for less than a fortnight prior to admission, and in Group 2 cases with symptoms since more than a fortnight prior to admission. Within either group the means of the paroxysms were computed for each day for the treated and control series, respectively. These data cover the period 2nd to and including 18th day after admission to hospital.

Results

The result of the treatment in Group 1 is presented in Fig. 1. Of the treated cases, 6 were in the catarrhal stage when the treatment was started, and of the controls, 7. In both curves a trend towards a milder course can possibly be traced for the treated series, but the difference is rather uncertain. It should be noted that even prior to institution of treatment, the frequency of paroxysms had been somewhat lower in the treated than in

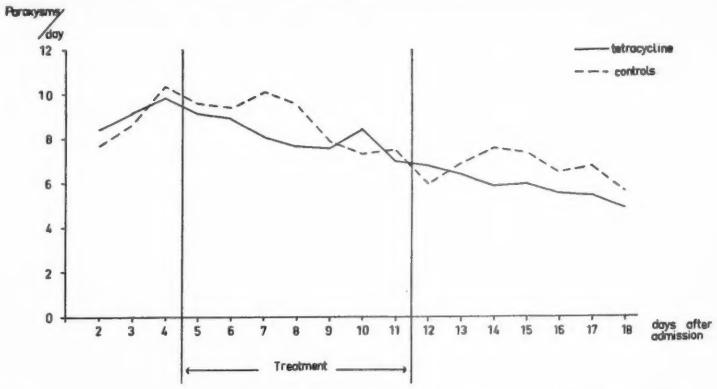

Fig. 2. Paroxysmal pertussis with more than a fortnight's symptoms prior to admission (none with more than 22 days' symptoms).
Treated: 31 cases with cough on an average 16.3 days prior to admission
Controls: 27 ,, ,, ,, ,, ,, ,, 18.5 ,, ,, ,, ,,

the control series. A comparison of exclusively catarrhal cases also fails to disclose any difference between treated and control cases.

The data pertaining to Group 2 are given in Fig. 2. On an average, in the control series the disease has arrived at a later stage (2 days), and conditions are thus somewhat more favourable than in the treated series. As will be seen from the figure, the course of illness is not influenced by treatment with Tetracyn.

The positive bacillary findings in the entire material are listed in Table 1. Owing to the small number of positive culture tests following termination of treatment even in the control group, no comparison is possible between the groups.

A patient in whom *H. pertussis* was demonstrated on admission, became free of bacilli after Tetracyn administration, but later on, in the 5th and 6th

TABLE 1

Number of cases with positive culture tests (*H. Pertussis*)

Cases	Before treatment	During treatment	After treatment	3rd week in hospital	4th week in hospital	5th week in hospital	6th week in hospital
Treated 54 cases	26 = 48%	4	1	—	—	1	1
Controls 42 cases	18 = 42%	6	—	1	—	—	1

TABLE 2

Complications

Cases	Pneumonia		Atelectasis		Acute otitis media		Bronchitis	
	Number	%	Number	%	Number	%	Number	%
Treated 54 cases	4	7.4	2	3.7	6	11.1	7	13.0
Controls 42 cases	6	14.3	2	4.8	2	4.8	6	14.3

weeks following admission, the organism was once again grown in cultures. At the same time an exacerbation of the disease and an increase in the number of "whoops" were observed. This may possibly have been due to depressed immunity owing to the treatment, and a reinfection of the patient in the ward. This has also been reported in connection with oxytetracycline treatment (Bogdan).

The types and incidence rates of complications supervening in the material are shown in Table 2. The pneumonia rate in the treated group is only one-half of that in the control group, but, on the other hand, the otitis rate is more than twice as high in the treated group. Sinusitis, catarrhal otitis media, pharyngitis etc. were equally common in both series. One case of encephalitis occurred in the control group. There were no fatalities.

Untoward Effects

There were few untoward effects associated with the treatment. Among 64 treated cases, diarrhoea occurred in 9, i.e. 14%.

In all instances stool cultures were made before, during, and after treatment as well as in the presence of loose stools. Among the 9 cases developing diarrhoea, *Staph. aureus*, though but sparsely, was present in the stools of two. In one case the normal intestinal flora was replaced by fungi. In the remaining cases, where no gastroenteric complications supervened, the normal intestinal flora decreased in the major proportion of instances, viz. yielding to enterococci and *Proteus*. In only one case vomiting occurred in direct connection with the administration of the drug.

Discussion

We have to conclude that in the present study tetracycline proved inefficacious in pertussis. There was no apparent pronounced tendency to undesirable effects, and the risk of the development of enterotoxin-producing

staphylococci in the stools was negligible. How, then, is the failure of the treatment to be explained? As has already been pointed out, encouraging results have been obtained with chlortetracycline and oxytetracycline, and hence tetracycline might reasonably be expected to act favourably on the disease. *In vitro*, no decisive difference was demonstrable between the three tetracyclines as regards inhibition of the growth of *H. pertussis*.

Poor absorption of the drug and too low a serum level might be blamed, but this explanation can safely be refuted on account of the dosage used by us, viz. 30 mg/kg body weight a day. Admittedly we have not performed estimations of serum concentration; however, e.g. Schwarzer *et al.* have shown that in children a single dose of 6 mg/kg body weight will maintain therapeutically efficient concentrations for 8 hours. During the second day of treatment a cumulative effect also is initiated.

The present material includes few children in the catarrhal stage at the start of treatment. Here one might possibly seek the explanation of the absolute failure. As has been shown by most workers, the best results are achieved when the antibiotics are instituted in the first week of illness. Unfortunately such a treatment is of limited practical value, since in the major proportion of instances, the diagnosis is not made until the "whoops" have commenced.

Summary

Fifty-four cases of whooping-cough were treated with tetracycline (Tetracyn). In 42 cases, serving as controls, a placebo was given. The dosage was 30 mg/kg body weight daily, divided into 4 doses. The course of the drug was started 4 days after admission and continued for 7 days. The effect of the treatment was assessed by the number of paroxysms and "whoops". The material was divided into two groups, one including cases where symptoms had been present for less than a fortnight prior to admission, and one with symptoms since more than a fortnight. In neither group was any effect of the Tetracyn treatment to be demonstrated. All but 2 of the treated cases were free of bacilli after termination of treatment. The incidence rates of complications were the same in the treated and control series. The treatment gave rise to few untoward effects. Transient diarrhoea occurred in 14 %.

Traitement de la Coqueluche par la tétracycline.

54 cas de Coqueluche ont été traités par la tétracycline (Tétracyn), et par comparaison, un groupe témoin de 42 cas reçut un placebo. La dose administrée fut de 30 mg/kg de poids, en 4 prises quotidiennes. Le médicament fut donné 4 jours après l'entrée, et pendant 7 jours. Aucun effet bénéfique ne fut enregistré, quelque soit le moment où le traitement fut commencé. Dans 14 % des cas, une diarrhée passagère fut observée.

Tetracyclinbehandlung des Keuchhustens.

54 Fälle von Keuchhusten wurden mit Tetracyclin (Tetracyn) behandelt und 42 Fällen, die als Kontrollen dienten, wurde ein Placebo gegeben. Die Dosierung betrug

30 mg/kg Körpergewicht täglich, aufgeteilt in 4 Dosen. Das Mittel wurde 4 Tage nach der Aufnahme eingesetzt und 7 Tage lang gegeben. Es konnte kein günstiger Effekt beobachtet werden, zu welcher Zeit auch mit der Behandlung begonnen wurde. In 14 % bestand eine vorübergehende Diarrhöe.

Tetraciclina en el tratamiento de la coqueluche.

Se trataron 54 casos de coqueluche con tetraciclina (Tetracyn) usándose otros 42 casos como grupo control, a los cuales se administró un placebo. La dosis fue de 30 mg/kg en las 24 horas dividido en cuatro tomas. La droga se administró a partir del cuarto día de admisión y fué continuada durante 7 días. No se pudo demostrar ningún efecto benéfico cualquiera haya sido el momento de comenzar el tratamiento. Diarrea pasajera ocurrió en el 14 % de los casos.

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The Influence of Heredity and Environment upon Stature in School Children

by FLEMMING QUAADE

It is universally agreed that we must pay attention to height when we want to estimate a child's physical development. But in order to make the right use of this criterion, we must know something of the factors that decide the stature of a child. This question has already been treated by numerous authors; it is difficult to evaluate the copious literature on the subject, but a review of some of the important contributions leaves one with the following general impressions:

(1) Stature—both of children and of adults—is one of the components that make up what we understand by *race*. As an extreme example it may be mentioned that the tallest pigmies are inferior in height to the shortest Dinkas. Of course, the racial differences are usually far less pronounced, and in a population like that of the U.S.A. there are no appreciable differences between the average heights for white and coloured children (Meredith). These problems need no further mention in this paper, as it deals exclusively with conditions in the Danish population which, from a racial point of view, is very homogenous.

(2) There can be no doubt that height is dependent upon *hereditary conditions* (Pearson & Lee, Davenport, Colin), but it must be added that the stature of children has received less attention than the pronounced correlation existing between parents' heights and the heights of their grown-up sons and daughters.

(3) *Environment*—in the widest sense of the word—exerts an influence on the stature of children. Abroad (Boas, Weisman, Meredith) as well as in Denmark (Nommels, Hansen, Hertz, Døssing), it has been found that on an average well-to-do children are taller than children from the poorer classes. Supplementary feedings of milk or fruit favour the growth of school children (Morgan & Warren, Roberts *et al.*). And adverse conditions, such as war and blockade, have temporarily caused a decrease in the average height of children, e.g. in Germany (Schlesinger, Coerper *et al.*) and Norway (Ström).

(4) We know that most serious *diseases* can inhibit the growth of children;

a few endocrine disorders lead to augmented height. I have considered i outside the scope of this investigation to evaluate individual morbidity, an I have not excluded any individual from the examined 'normal population of school children.

(5) Results of measurements will depend upon the *time* of the investiga tion. On an average, both foreign and Danish children are taller now tha children were in the beginning of the century (Hansen, Gray, Hultkrantz Lloyd-Jones, Meredith). Primarily, this seems due to an improved enviro ment (improved nutrition, prophylaxis and treatment of disease), but w cannot quite disregard the possibility that some 'selection of the fittest' may play a certain role—even if modern society endeavours to protec the physically handicapped.

Although we know a great deal about all these factors—hereditary o external—and their influence upon the height of children, it must still b admitted that up till now literature has left some questions unanswered especially as regards the relative importance of nature and nurture within one population. It is e.g. possible that stature of pre-puberal children is correlated more closely with environment than with parents' heights, and that they do not range themselves in hereditarily determined height groups until after the puberal acceleration of growth. Or we might imagine, in a Scandinavian country, that environment has improved so much during the last decades that even the least well-to-do children have obtained the external conditions necessary for letting them grow as tall as their heredity will permit them; in other words, that the latter has become totally dominating, and that social environment is unimportant, provided it is above a certain minimum.

It has therefore been my aim and purpose to make a comparative study in the present Danish population of the two factors heredity (expressed by parents' heights) and environment (expressed by the income of the breadwinner) in their influence on the stature of growing individuals.

The investigation comprises the aggregate population (3771 children 6–16 years of age) who frequented four Copenhagen City Council schools during the year 1949–50. The schools were selected so as to represent all social strata. The height measurements and the ages of the children were registered from the school health cards, and all parents were requested by letter to inform me of their heights and their approximate annual incomes. It goes without saying that we can only ascribe a limited accuracy to the parents' answers in each single case, but this fact can hardly be supposed to alter the main lines in the statistical evaluation. It would be much more important to make sure that no undesirable selection from the material should take place due to the fact that only 1629 families gave satisfactory answers to my questions. But as we shall see later, my conclusions can only be questioned in case the alternatives: answer/no answer should be linked together with certain *combinations* of the examined criteria.

TABLE 1

Relations between height indices of children and breadwinners within five income groups.

Height index of child	Height index of breadwinner					Total	Income D. Kr.
	1	2	3	4	5		
1	5	16	7	0	2	30	
2	5	18	16	6	3	48	
3	6	15	18	14	6	59	
4	1	3	8	4	10	26	< 6,000
Total	17	52	49	24	21	163	
Average height index	2.18	2.10	2.55	2.91	3.14		
1	18	21	11	6	0	56	
2	35	45	49	38	7	174	
3	20	54	60	48	24	206	
4	5	27	33	51	27	143	6,000–8,000
Total	78	147	153	143	58	579	
Average height index	2.15	2.59	2.75	3.00	3.34		
1	6	19	11	3	2	41	
2	14	27	41	27	8	117	
3	13	43	77	47	26	206	
4	6	15	41	26	23	111	8,000–10,000
Total	39	104	170	103	59	475	
Average height index	2.49	2.52	2.87	2.93	3.19		
1	6	3	3	2	0	14	
2	4	17	28	10	2	61	
3	8	23	30	22	8	91	
4	3	11	20	17	26	77	10,000–12,000
Total	21	54	81	51	36	243	
Average height index	2.38	2.78	2.83	3.06	3.67		
1	0	2	1	0	1	4	
2	4	9	14	10	6	43	
3	3	14	19	18	12	66	
4	0	8	10	21	17	56	> 12,000
Total	7	33	44	49	36	169	
Average height index	2.43	2.85	2.86	3.22	3.25		

TABLE 1 A

Computation of correlation coefficient for Table 1.

Annual income (D. Kr.) of breadwinner	r	$\log \frac{1+r}{1-r}$	$n-3$
< 6.000	0.371	0.338	160
6,000–8,000	0.343	0.311	576
8,000–10,000	0.237	0.210	472
10,000–12,000	0.357	0.324	240
> 12,000	0.250	0.222	166
Total	0.308	0.277	1,614

Average value of $z = 1.1513 \times 0.277 = 0.319$
$t = 0.319 \sqrt{1614} = 12.76$ $r = 0.308$

And it seems improbable that the simultaneous existence of tall children and low income (or the reverse constellation: short children and high income) should influence the parents' willingness to answer the questions.

The measurements of the children were compared with the values given by Døssing in his age–height tables for Copenhagen school children in 1950. Each child was characterized by a "height index" from 1 to 4:

1: Height below (mean value − standard deviation).
2: Height between mean value and (mean value − standard deviation).
3: Height between mean value and (mean value + standard deviation).
4: Height above (men value + standard deviation).

I have not divided the material according to sex, as there proved to be no differences between boys and girls regarding the criteria examined here.

The parents were given height indices from 1 to 5:

	Fathers (cm)	Mothers (cm)
1	≤ 165	≤ 155
2	166–170	156–160
3	171–175	161–165
4	176–180	166–170
5	> 180	> 170

Fisher, among others, has described the statistical method used in calculating the following correlation coefficients.

Table 1 and 1 A show how the children's indices are distributed according to height index of breadwinner (usually father) when the material is divided into income groups. It will be seen that there is a very strong correlation between the heights of breadwinner and child, and this connection is found on all income levels. Tables 2 and 2 A show the distribution of children's indices according to breadwinners' incomes; this time the material is divided into groups of parents' heights. There is a clear correlation between the

TABLE 2

Relations between height index of child and approximate annual income of breadwinner, the material being divided up into five groups of height index for breadwinner.

Height index of child	Annual income					Total	Height index of breadwinner
	5,000	7,000	9,000	11,000	13,000		
1	5	18	6	6	0	35	
2	5	35	14	4	4	62	
3	6	20	13	8	3	50	
4	1	5	6	3	0	15	1
Total	17	78	39	21	7	162	
Average height index	2.18	2.15	2.49	2.38	2.43		
1	16	21	19	3	2	61	
2	18	45	27	17	9	116	
3	15	54	43	23	14	149	
4	3	27	15	11	8	64	2
Total	52	147	104	54	33	390	
Average height index	2.10	2.59	2.52	2.78	2.85		
1	7	11	11	3	1	33	
2	16	49	41	28	14	148	
3	18	60	77	30	19	204	
4	8	33	41	20	10	112	3
Total	49	153	170	81	44	497	
Average height index	2.55	2.75	2.87	2.83	2.86		
1	0	6	3	2	0	11	
2	6	38	27	10	10	91	
3	14	48	47	22	18	149	
4	4	51	26	17	21	119	4
Total	24	143	103	51	49	370	
Average height index	2.91	3.00	2.93	3.06	3.22		
1	2	0	2	0	1	5	
2	3	7	8	2	6	26	
3	6	24	26	8	12	76	
4	10	27	23	26	17	103	5
Total	21	58	59	36	36	210	
Average height index	3.14	3.34	3.19	3.67	3.25		

TABLE 2 A

Computation of correlation coefficient for Table 2.

Height index of breadwinner	r	$\log \frac{1+r}{1-r}$	$n-3$
1	0.120	0.1047	159
2	0.177	0.1554	387
3	0.084	0.0731	494
4	0.082	0.0714	367
5	0.066	0.0574	207
Total	0.107	0.0935	1,614

Average value of $z = 1.1513 \times 0.0935 = 0.108$
$t = 0.108 \sqrt{1614} = 4.32$ $r = 0.107$

height of the child and the size of the income, and this appears within all height groups of parents. Thus, in Table 1 the connection between children's and breadwinners' statures is treated irrespective of the economical factor; in Table 2 we compare children's heights with incomes, statures of breadwinners remaining constant. This grouping of the material enables us to estimate the relative importance for children's heights of heredity and environment, represented by breadwinners' heights and breadwinners' incomes respectively. The two correlation coefficients given in Tables 1 A and 2 A—0.308 and 0.107—are both strongly significant, but it will be seen that the connection between children's and breadwinners' indices is particularly striking. We need only compare the Fig. 1 and 2, which illustrate the contents of Tables 1 and 2.

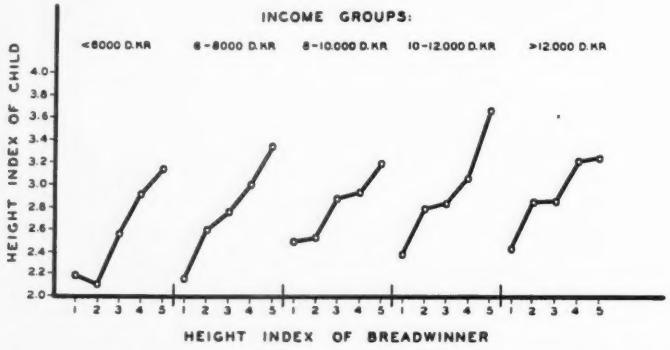

Fig. 1. The average height index of children in its variation with height index of breadwinner within five income groups.

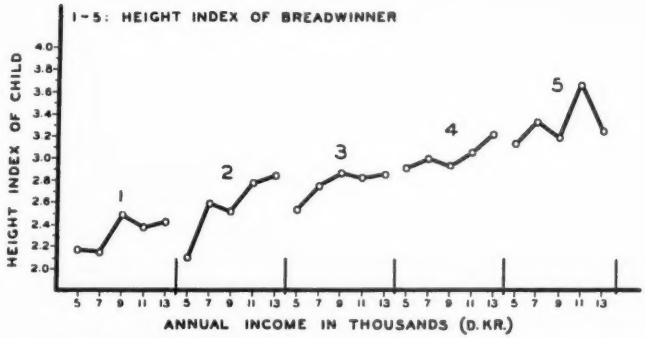

Fig. 2. The average height index of children in its variation with breadwinners' annual incomes within five groups of breadwinners' heights.

In Fig. 1 the steepness of each single curve expresses the strong correlation between children's and breadwinners' heights; the much slower rise from left to right in the joint level of the curves is due to the influence of the economical factor. Conversely, we find in Fig. 2 a moderate obliquity in each single curve—caused by income levels—but a strong crescendo in the five curves viewed as one—the influence of breadwinners' heights.

Table 3 further illustrates the hereditary factor:

TABLE 3

Average height indices for the children when the latter are divided into groups according to nine combinations of parents' heights. The parentheses give the numbers of children in each group.

	Mother small (< 155 cm)	Mother medium (155–170 cm)	Mother tall (> 170 cm)
Father small (< 165 cm)	1.80 (20)	2.31 (108)	(4.00) (1)
Father medium (165–180 cm)	2.26 (86)	2.78 (1359)	3.13 (83)
Father tall (> 180 cm)	3.00 (5)	3.23 (203)	3.53 (40)

In Table 3 the materials of mothers and fathers are each divided into three groups: small, medium, and tall; and the average height index of the children is computed for each of the nine possible matrimonial combinations. There

TABLE 4

The relation between breadwinners' height indices and approximate annual incomes in Danish Kroner.

Income (D. Kr.)	Height index of breadwinner					Total
	1	2	3	4	5	
< 6,000	17	52	49	24	21	163
6,000–8,000	78	147	153	143	58	579
8,000–10,000	39	104	170	103	59	475
10,000–12,000	21	54	81	51	36	243
> 12,000	7	33	44	49	36	169
Total	162	390	497	370	210	1629
Average income	8.040	8.320	8.670	8.780	9.080	8.600

$$r = \frac{548}{\sqrt{2244 \times 8342}} = 0.127$$

$$t = \frac{0.127}{\sqrt{1 - 0.0161}} \sqrt{1627} = 5.17$$

is a clear correlation between the height of the child and that of its father irrespective of mother's height; at the same time we find an equally strong connection between child's and mother's heights independent of father's height. The smallest average index is found in children of two small parents, whereas the tallest children are those that have a tall father as well as a tall mother. The table also shows that men and women tend to choose matrimonial partners whose heights harmonize with their own.

Finally we shall see that there is a distinct correlation between income and height also where adults are concerned (Table 4).

It is difficult to explain cause and effect in this relationship; some well-to-do men are certainly tall because they have grown up in wealthy families (cp. Table 2); on the other hand, we can hardly doubt that tallness—if it is a manifestation of physical superiority—favours the possibilities of a high income. We must remember that the majority of breadwinners in a normal population are employed in some sort of manual work.

This article deals only with some of the factors that show a relationship with the stature of children in a mass-investigation, and it does of course not tell us what is decisive for each individual child; still we are justified in making the following conclusive remarks:

It is characteristic that usually all the relevant factors act in the same direction: the tallness of men is apt to reproduce itself in tall children, so is

the tallness of women; these men and women are liable to find one another in marriage, thus augmenting the hereditary probability of producing tall children; furthermore, the tall breadwinners often earn so much that favourable surroundings can add even more to the heights of the children. A similar line of thought applies to the other extreme, the families with short members and low incomes. Naturally, most fathers are of medium height; they marry medium women and beget medium children, and though their medium incomes cannot produce optimal growth in the children, it does not, on the other hand, work as a serious impediment.

Deviations from this typical pattern tend to modify children's heights, and here it seems that the impact of heredity is much more decisive than that of environment.

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Summary

The material comprises 1629 children from four Copenhagen City Council schools, selected so as to represent all social strata. Statistical evaluation reveals the following very clear correlations:

(1) child's height ~ breadwinner's height—irrespective of income level; (2) child's height ~ breadwinner's income—irrespective of breadwinner's height; (3) father's height ~ mother's height; (4) father's height ~ child's height—irrespective of mother's height; (5) mother's height ~ child's height—irrespective of father's height; (6) breadwinner's height ~ breadwinner's income. The correlation coefficient for (1) is decidedly greater than for (2).

The following conclusions are drawn: the tallness of men is apt to reproduce itself in tall children; so is the tallness of women; such men and women tend to choose one another in marriage, thus augmenting the hereditary probability of producing tall children; furthermore, tall breadwinners are liable to earn so much that a favourable environment can add even more to the heights of the children. A similar line of thought applies to families with short members and low incomes. In the nature of things, the majority of men are of medium height; they marry medium women and beget medium children, and their medium incomes, though not optimal for the growth of the children, do, on the other hand, not act as a serious impediment. Deviations from these typical patterns tend to modify the children's heights, and here it seems that the impact of heredity is much more forcible than that of the environment.

Influence de l'hérédité et du milieu sur le développement des enfants en milieu scolaire.

La taille du père influe sur le développement statural de ses enfants, ainsi que celle de la mère. Comme en outre, les hommes de haute taille ont tendance à choisir comme compagnes des femmes de taille équivalente, ce fait augmente encore les chances d'une

descendance de taille également supérieure à la normale. Si l'on ajoute que des soutiens de famille d'une taille élevée ont généralement des revenus supérieurs à la normale, le milieu dans lequel ils vivent peut encore accroitre la taille des enfants. Des causes identiques s'appliquent aux familles d'une taille faible, et à revenus bas. Cependant, la majorité d'une population est de taille moyenne. Les hommes épousent des femmes de taille moyenne, donnent naissance à des enfants de taille moyenne, et leurs revenus moyens, s'ils ne constituent pas une circonstance favorable au développement morphologique de leur descendance, ne constituent pas non plus un obstacle. Des modifications à ce schéma standard, peuvent entrainer des différences dans la stature des enfants : Dans ces anomalies il semble que le facteur héréditaire soit nettement plus important que le facteur milieu.

Der Einfluss der Heredität und der Umgebung auf den Wuchs der Schulkinder.

Die Grösse des Vaters wie die der Mutter bestimmt den Grössenwuchs der Kinder. Hochgewachsene Männer und Frauen haben die Tendenz, sich gegenseitig zur Ehe zu wählen, was die hereditäre Wahrscheinlichkeit zur Zeugung grosser Kinder noch verstärkt. Weiterhin sind hochgewachsene Ernährer in der Lage, so viel zu verdienen, dass eine günstige Umgebung noch mehr zur Grösse der Kinder beitragen kann. Eine entsprechende Ursachenverknüpfung macht sich bei Familien mit kleinwüchsigen Mitgliedern und niedrigem Einkommen geltend. Natürlicherweise ist die Mehrzahl der Männer von mittlerer Höhe; sie heiraten mittelgrosse Frauen, haben mittelgrosse Kinder und ihr mittelmässiges Einkommen wirkt, obgleich es nicht optimal für das Wachstum der Kinder ist, andererseits nicht als ernste Behinderung. Abweichungen von diesen typischen Befunden können die Grösse der Kinder beeinflussen und es scheint dann, als wäre der Faktor der Heredität deutlich zwingender als der der Umgebung.

La influencia de la herencia y del medio sobre la estatura de los niños en edad escolar.

La talla del padre y de la madre influyen sobre el desarrollo estatural de los hijos. Como los hombres de gran talla tienden a elegir mujeres altas como compañeras, este hecho aumenta las posibilidades de una descendencia de estatura superior a la normal. Si se acepta que un hombre alto tiene mejores posibilidades de obtener buenos trabajos, el medio que ellos proporcionan a sus hijos contribuye también a aumentar la talla de estos. Causas idénticas son aplicables a familias de talla pequeña y entradas bajas. Pero en la realidad cotidiana, hombres medianos se casan con mujeres medianas y dan productos también de talla media y aunque sus entradas medianas no producen un efecto favorable en el desarrollo morfológico de su descendencia, no constituyen tampoco un obstáculo. Desviaciones de este esquema standard tienden a modificar la estatura de los niños; aquí aparece el factor hereditario como mas importante que el factor medio ambiente.

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Exanthema Subitum and Febrile Convulsions

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So far it is not known if any special diseases dispose to so-called febrile convulsions, the origin of which is subject to controversies. The intention of this paper is to point out to what extent exanthema subitum may be involved in this connection.

The Frequency of Febrile Convulsions

It is generally agreed that febrile convulsions are common in children. In well baby clinics 4.2 % of the children had attacks of convulsions during the first five years of life, 41 % of these in connection with fever (Patric & Levy). According to Peterman (14), one-third of all convulsions in children appears in connection with or is caused by a fever, and 1.9 % of all children treated in hospital have febrile convulsions. Out of 3781 children younger than seven years who were admitted to hospital in Copenhagen, 40 % were febrile, and of these each ninth child had febrile convulsions (Friderichsen & Melchior).

Age

In Herlitz' 776 cases of febrile convulsions, the median was 18 months, $^1/_4$ was younger than 11 months and $^1/_4$ older than 29 months. Friderichsen & Melchior also found a maximum at 18 months among their 465 cases; 82 % had not reached the age of three years, but there were seldom any cases of genuine febrile convulsions at ages under six months. In M. A. Lennox' compilation of 311 cases of febrile convulsions all except 4 % were younger than 4 years.

Heredity

Convulsions are only caused by infection and fever in children who have a potential convulsive state (Peterman, 14). Affected children have a hereditary convulsive tendency (Herlitz; Peterman, 15). Only 3 % of children with a fever have a hereditary history of convulsions, while in cases with febrile convulsions there are convulsions in the family in 45 % (Lennox, 9). Epilepsy in the family occurs twice as often in children with febrile convulsions; this is genuine epilepsy, but with a tendency to disappear quickly owing to the stabilizing effect of age (Lennox, 10).

The Importance of Fever

Wegman managed to elicit convulsions in kittens by heating them in a thermoelectric chamber, if the kittens were neither younger than 4 nor older than 8 weeks. The result depended on the speed of the heating and the rate of the temperature.

Lennox, Sibley & Zimmerman could point out cellular damages to the brain in kittens treated likewise. The higher the temperature, the greater is the risk of getting febrile convulsions which seldom occur at a temperature below 38.5°C (Herlitz). Febrile convulsions appear most often when the temperature is rising or when it has reached a peak. It is very likely that the rapidly increasing temperature is the most dangerous with respect to convulsions (Lennox, 10). Friderichsen & Melchior believe that a high temperature is not necessary to cause convulsions. In their material, 11.1 % of the cases had a temperature not exceeding 37.9°C on admission to hospital. According to Lennox (10), both fever and convulsions can be caused by an infectious, toxic damage of the cerebral cells. Infection and fever together cause convulsions. Merely fever, e.g. in cerebral damage, cerebral operations, malignant tumour, allergy, etc., seldom causes febrile convulsions.

Further Theories on the Genesis of Febrile Convulsions

According to Herlitz, febrile convulsions are due to a sudden disturbance of the cerebral circulation by an active anaemia accompanied by hyperaemia of the brain, the vessels of which are constitutionally sensitive. The electroencephalogram, in 74 % of cases of febrile convulsions, shows signs of an organic brain lesion (Peterman, 15). Lenggenhager believes that when infants have a fever, a respiratory alkalosis appears which in connection with hyperthermia causes febrile convulsions identical to heat-stroke in adults.

The Nature of the Infection

In Herlitz' material the cause of the fever was stated as pharyngitis in 79.6 %; acute pulmonary affection in 5.8 %; otitis, pyelitis, erysipelas etc. in 2.8 %; and epidemic children's diseases as, for instance, parotitis, morbilli, rubella and exanthema subitum, in 2.6 %. Out of 1016 cases of scarlet fever who were younger than six years, 0.5 % had febrile convulsions. In Friderichsen & Melchior's material, tonsillitis and infection in the upper airways were present in 62.4 %; otitis in 11.4 %; bronchitis and pneumonia in 9.9 % and pyuria in 0.6 %. Exanthema subitum is not mentioned. Livingstone reports 201 patients with febrile convulsions; the cause of fever was exanthema subitum in 8 cases.

Lennox (10) has dealt with the cause of fever and febrile convulsions. If it were the actual infection and its circulating toxins which cause febrile convulsions, then certain infections would be the cause of these convulsions more often than others. It is possible that the respiratory tract diseases dominate in the febrile convulsion material because of their frequency.

Febrile Convulsions in Exanthema Subitum (E.S.)

The frequency of febrile convulsions in E.S. varies considerably according to different authors.

Clemens, for instance, found no case of febrile convulsions among 80 cases of E.S., and Rosenbuch (224 cases) considers convulsions as comparatively rare in connection with this disease.

Zahorsky (22) points out that the onset of E.S. in several cases was violent and combined with febrile convulsions. Barneberg & Greenspan

observed an E.S. epidemic in an orphanage, where one aut of 54 cases go febrile convulsions. Greenthal has seen 100 cases of E.S., six of them witl convulsions. Windorfer had 117 cases, 35 of which had febrile convulsions an Glanzmann also observed several severe convulsions. Vahlquist believes tha attacks of convulsions are rather usual as an alarming onset, and 8 of hi reported 35 children treated in hospital for E.S. were admitted because o convulsions at the onset of the disease. He is not sure whether it is a matte of "simple febrile convulsions" or not.

According to Posson all physicians with any experience of E.S. must agre that this is a common cause of febrile convulsions during the second yea of life. He believes it to be possible that, beside the febrile effect, the in fection has a selective influence on the brain. In three cases with norma findings at lumbar puncture, he observed a hemiplegic weakness after severe attacks of convulsions, a complication which is perhaps more usual than was previously believed. Windorfer's train of thougth is similar. He believes that convulsions with E.S. are not only ordinary febrile convulsions but a facultative symptom of the disease depending on meningo-encephalitic processes. In four of his cases paresis occurred. Persisting cerebral changes, which later on may elicit new attacks of convulsions, are to be dreaded. Glanzmann, as well as Windorfer, points out that children with E.S. seem to show signs of cerebral affection. They toss to and fro, vomit, are tender to touch, and older children complain of a headache. He believes that a serous meningitis is present in many cases with a bulging fontanel and increased liquor pressure. He has seen one case of hemiparesis after convulsions in E.S. Zahorsky (21) points out that the liquor pressure may be increased while the cell and albumin values are normal.

Own Case Material

During 1945–1954, 448 children were treated at the Children's Hospital, Gothenburg, for febrile convulsions (in cases of a recurrence, only the first admission has been included). During this period a total of 29,999 children aged up to 16 years were admitted. The cases of febrile convulsion amount to 1.5% of the admitted children.

The age median of the patients with febrile convulsions is 19.5 months, the youngest being one month and the oldest nine years and two months; 9 or 2.0% were younger than six months and 13 or 2.9% were older than five years.

The highest temperature measured during the day of admission was, on an average, 39.6°C.

The cases of febrile convulsion were divided into different groups according to the following diagnoses:

Pharyngitis	79.9 %
Exanthema subitum (34 cases)	*7.6* %
Bronchitis, bronchopneumonia	3.6 %
Otitis	1.8 %
Dyspepsia	1.6 %
Pyelitis	1.1 %
Other diseases	4.4 %

Children with epidemic diseases were admitted in exceptional cases only. Many cases of otitis are also treated in other hospitals.

Two hundred and sixteen children were 18 months old or younger, of these 12.0% had exanthema subitum. One hundred and five children were 12 months old or younger and 16.2% of these had exanthema subitum.

The diagnosis exanthema subitum has been made on the basis of an exanthema of typical appearance, occurring after the fever had declined, and a typical change in the blood picture. The white cell count after the decrease of temperature averaged 5447 (in 8 cases < 4000), and the percentage of lymphocytes 76.1 (in 13 cases > 80).

During 1949 and 1952 an investigation was made regarding the number of children who were admitted to the hospital between the ages of six months and five years and with a maximum temperature of $\geqq 39°C$. The dispersion of diagnoses and the febrile convulsions (in per cent) are shown in Table 1.

The 34 cases of E.S. with febrile convulsions are rather evenly distributed over the ten years included in the investigation. No pronounced seasonal variation has been found. At the same time 91 cases of E.S. without convulsions were admitted.

The median age for the 34 cases was 12.5 months, the youngest age was three months, and the highest three years and eight months. The age median for the remaining 414 cases of febrile convulsions was 20.8 months.

A lumbar puncture was performed in 29 cases on the children with E.S. and convulsions. Six cases were considered to have an increased liquor pressure. The white cell count per cmm liquor was 5 in two cases and 9 in one case.

Later on, at least two of the children had repeated attacks of convulsions in connection with fever. One child, the one with 9 white cells in the liquor, later developed a very troublesome grand mal epilepsy with attacks even without fever. In this case there is no convulsive heredity, no signs of cerebral lesions and the electroencephalogram is considered normal.

Discussion and Conclusions

From the present investigation it is seen that exanthema subitum accounted for almost 8% of the cases treated for febrile convulsions at the Children's Hospital, Gothenburg, during a ten-year period. If the children

TABLE 1

The dispersion, according to diagnoses, of the children between six months and five years admitted during 1949 and 1952 with a temperature $\geqq 39°C$. The number of febrile convulsions in the different groups of diseases.

Diagnoses	Number of cases	Per cent	Cases with febrile convulsions	
			Number	Per cent
Pneumonia, bronchitis	171	34.8	2	1.2
Pharyngitis, angina	168	34.0	54	32.1
Exanthema subitum	*18*	*3.6*	*5*	*27.8*
Dyspepsia	22	4.5	1	4.5
Otitis	42	8.5	2	4.8
Pyelitis	23	4.7		
Meningitis	17	3.4		
Other cause of fever	32	6.5		
Total	493		64	13.0

admitted with febrile convulsions were 12 months or younger, this percentage amounted to fully 16. Furthermore, among the cases of febrile convulsions in which pharyngitis etc. were believed to be the cause of fever, there are probably some cases of undiagnosed exanthema subitum.

In several previously published statistics of febrile convulsions, exanthema subitum is of little or no importance. It seems to be quite out of the question that Gothenburg should have a larger frequency of exanthema subitum. My experience from other Swedish children's hospitals is that exanthema subitum with febrile convulsions is not an unusual diagnosis. Exanthema subitum is a comparatively "new" disease, which started being diagnosed to a large extent only after Zahorsky published his papers in the 1910's. If there is no suspicion of this disease, the diagnosis will be atypical morbilli or rubella or else pharyngitis, influenza etc., and the eruption is neglected or interpreted as a "febrile eruption", or as one caused by drugs etc.

Some authors have observed that exanthema subitum often causes febrile convulsions, while others have not noticed this connection. The explanation may be that exanthema subitum during the first years of life is a very frequent cause of fever, which, like other diseases, sometimes elicits febrile convulsions. The hospital physicians take care of the most severely affected children and thus obtain a large percentage of exanthema subitum with convulsions in their material.

Some facts, however, suggest that exanthema subitum does not cause convulsions merely through fever, but that a specific cerebral disturbance

occurs at the same time. Several other usual diseases with a high temperature, e.g. bronchopneumonia or pyelitis, comparatively seldom cause febrile convulsions. A few authors have pointed out that children with exanthema subitum seem to show cerebral affection; in some cases of convulsions, there were pathologic liquor findings, and paresis may appear in connection with the convulsions.

I agree that convulsions in exanthema subitum is a facultative symptom of the disease. It is possible that exanthema subitum may cause a persisting cerebral lesion which results in new convulsions later on. The experience of my cases may point to this fact.

Summary

Out of 448 cases of febrile convulsions admitted to the Children's Hospital, Gothenburg, during 1945–1954, at least 7.6 % (34 cases) occurred in connection with exanthema subitum.

Among the children with febrile convulsions who were 12 months old or younger, exanthema subitum was the cause of fever in 16.2 %.

The 34 cases of exanthema subitum had a median age of 12.5 months, the remaining 414 children with convulsions had a median of 20.8 months.

Exanthema subitum is supposed to cause convulsions not only because of fever, but because of a specific cerebral effect.

Persisting cerebral lesions may occur, resulting in new attacks of convulsion later on.

Exanthème subit et convulsions fébriles.

Sur 448 cas de convulsions fébriles admis à l'hopital de Gothembourg au cours des années 1945 à 1954, 7,6 % d'entr'eux au moins présentaient une association avec un exanthème subit. Cet exanthème était la cause de l'hyperpyrexie dans 16,2 % des cas, chez les enfants d'un âge égal ou supérieur à 12 mois. L'âge moyen des enfants présentant de l'exanthème subit était de 12,5 mois, et celui des autres de 20,8 mois. L'exanthème subit semble être la cause des convulsions; non, par la fièvre qui s'y associe, mais en raison d'une atteinte cérébrale spécifique. Des lésions cérébrales peuvent d'ailleurs persister, provoquant de nouveaux accés convulsifs, ultérieurement.

Exanthema subitum und Fieberkrämpfe.

Unter 448 Fällen von febrilen Krämpfen, die in der Kinderklinik in Göteborg in den Jahren 1945–54 aufgenommen wurden, traten 7,6 % in Verbindung mit Exanthema subitum auf. Unter den Kindern, die 12 Monate oder jünger waren, war in 16,2 % Exanthema subitum die Ursache des Fiebers. Das Durchschnittsalter der Kinder mit Exanthema subitum war 12,5 Monate, das der anderen 20,8 Monate. Es wird angenommen, dass das Exanthema subitum nicht allein auf Grund des Fiebers die Krämpfe verursacht, sondern durch eine spezifische cerebrale Affektion. Bleibende cerebrale Schäden können vorkommen, die später neue Krampfattacken hervorrufen.

Exantema súbito y convulsiones febriles.

Durante el período 1945–54 fueron admitidos, en el Hospital de niños de Gotemburgo, 448 casos de convulsiones febriles; 7,6 % de estas ocurrieron en relación con

exantema súbito. Exantema súbito fué la causa de fiebre en el 16,2 % de los lactantes hasta 12 meses de edad. La edad media de niños con exantema súbito fué 12,5 meses, siendo 20,8 meses para el resto. Esta afección se acompanaría de convulsiones no solo a causa de la fiebre sino por una afección cerebral específica. Lesiones cerebrales persistentes pueden ocurrir, siendo su resultado futuros ataques convulsivos.

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Determination of the Functional Residual Capacity in Newborn Infants

Preliminary Report

by GUNILLA BERGLUND and PETTER KARLBERG

This report describes a method of determining the functional residual capacity in newborn infants and some preliminary results are given. During respiratory studies on newborn infants (Karlberg *et al.*, Cook *et al.*) it was found of interest to be able to determine also the functional residual capacity. Different methods for use on adults and older children are available in the literature, but we have not been able to find any method applied to newborns.

Method

The closed-circuit method with helium as test gas has been used (Meneely & Kaltreider 1941, Willmon & Benke, Gilson & Hugh-Jones), and the volume was kept constant by a continuous addition of oxygen (Herrold & McMicheal, Engström *et al.*).

The closed system consists of the following components, connected in series in the direction of the gas circulation (see Fig. 1): a circulation pump (membrane type, capacity about 4 litres per minute), a carbon dioxide filter (soda lime), a humidifier, a katharometer for determining the helium concentration (with indicator by the Cambridge Instrument Co., reading up to a fraction of 0.20 in 0.002 divisions), a Benedict-Rooth spirometer (max. capacity 700 ml) recorded on a kymograph with an accuracy of 1 mm = 4 ml, a water seal for administration of helium, oxygen and air, and a double valve for closing the system and for connection with the baby. The whole system has a minimum volume of approximately 130 ml (determined as described in another publication by Engström *et al.*).

As practically all healthy quiet newborns like to breathe through their nose, a face mask has been constructed which collects the ventilation through the nose only. The mask, stretched around the baby's greased face and fixed at the neck with a hemostat, consists of a thin rubber sheet with two holes, one for the mouth and one for the nose. The mouth hole is open; over the nose hole a rubber tube (diameter 10 mm) with a corresponding sidehole is glued. Either the circulation pump in the system or a twin pump, when the baby is breathing fresh air in the beginning of the determination, keeps the gas in the rubber tube flowing constantly. In this way the dead space in the mask is negligible. The babies stand the maskbreathing very well. As the mask has a

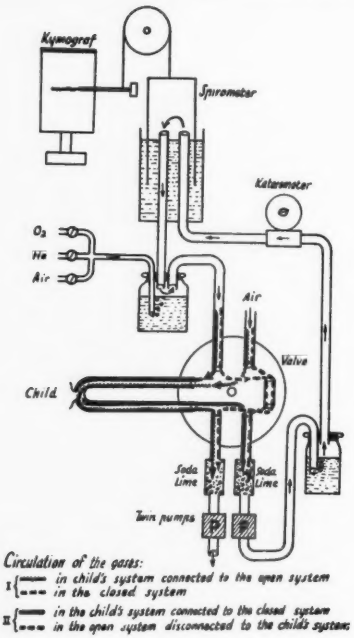

Fig. 1. Schematic diagram of the apparatus.

mouth hole, it is quite safe if the baby, for some reason, should like to cry. On the other hand, even a very small leak through the mouth will be immediately detected from the kymograph tracing and the katharometer readings.

Procedure

The closed system is first filled with a gas-mixture of 21 vol % O_2, 19–20 vol % He and the balance of N_2. After thorough mixing, the He fraction and the spriometer volume are accurately recorded. During this time the baby is breathing fresh air through the mask. The baby's respiratory tract and the mask–tube volume (a known constant volume) are connected by means of the double valve to the closed system and increase the volume of the closed system. Because of this the helium concentration will decrease towards an equilibrium level. During this time the baby's oxygen consumption is compensated for by continuous addition of oxygen so that the closed system has a constant volume. The helium concentration is read every minute and, when constant readings during even breathing and the maintenance of a constant volume have been obtained for 3–4 minutes, there is sufficient information.

Fig. 2 shows a typical record and the calculation of the functional residual capacity, which is corrected to BTPS.

The method is continuously checked by determining the volume of glass bottles with a known volume in the babies' range and by double determinations on the babies.

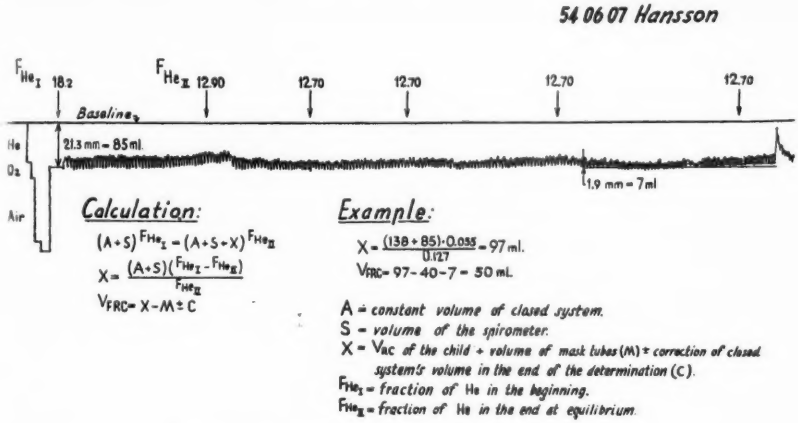
54 06 07 Hansson
F_{He_I} 18.2
$F_{He_{II}}$ 12.90
12.70
12.70
12.70
12.70
Baseline
He
O2
Air
21.3 mm = 85 ml.
1.9 mm = 7 ml
Calculation:
$(A+S)F_{He_I} = (A+S-X)F_{He_{II}}$
$X = \frac{(A+S)(F_{He_I} - F_{He_{II}})}{F_{He_{II}}}$
$V_{FRC} = X - M \pm C$
Example:
$X = \frac{(138+85)\cdot 0.055}{0.127} = 97$ ml.
$V_{FRC} = 97 - 40 - 7 = 50$ mL.
A = constant volume of closed system.
S = volume of the spirometer.
X = V_{AC} of the child + volume of mask tubes (M) ± correction of closed system's volume in the end of the determination (C).
F_{He_I} = fraction of He in the beginning.
$F_{He_{II}}$ = fraction of He in the end at equilibrium.

Fig. 2. A typical record with calculations.

Preliminary Results

Twelve healthy newborns of ages ½–7 days have been examined (Fig. 3). The obtained values are graphically related to the birthweights showing a good positive correlation. A newborn baby with a birth weight of 3.5 kg has about 95 ml in functional residual capacity. In regard to the BMB line, a newborn has a 2½ times lower value in comparison with an adult, which corresponds very well to other lung functions in the newborns (Cook *et al.*).

Three newborns with marked lung atelectasis judged by clinical examination and chest X-ray films are found to have definitely smaller VFRC than the healthy babies. The investigation is in progress.

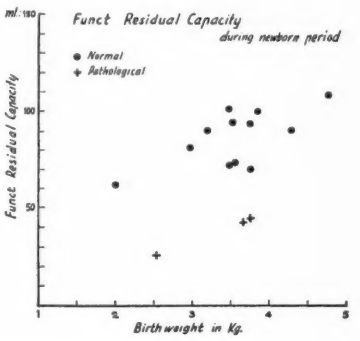

Fig. 3. A diagram showing the relationship between functional residual capacity and birthweight in newborn infants, age ½–7 days.

Summary

A method for determining the functional residual capacity in newborn infants is described. Preliminary results show that the newborns have relatively about 2½ times lower values than adults.

Mesure de la capacité résiduelle fonctionnelle chez le nouveau-né. Résultats préliminaires.

Description d'une méthode de mesure de la capacité résiduelle fonctionnelle. Les premiers résultats indiquent que les chiffres obtenus chez les nouveaux-nés sont environ 2½ fois plus faibles que ceux de l'adulte.

Bestimmung der funktionellen Residualluft bei Neugeborenen. Vorläufiger Bericht.

Es wird eine Methode zur Bestimmung der funktionellen Residualluft bei Neugeborenen beschrieben. Vorläufige Resultate zeigen, dass Neugeborene etwa 2½mal relativ niedrigere Werte haben als Erwachsene.

Determinación de la capacidad functional residual en el recién nacido. Comunicación preliminar.

Se describe un método para determinar la capacidad funcional residual en el recién nacido. Los estudios preliminares mostraron que el recién nacido tiene relativamente una capacidad residual funcional alrededor de 2½ veces menor a la del adulto.

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Renal Thrombosis in the Newborn

Report of a "Primary" Case Successfully Treated by Surgery

by E. TVETERÅS and P. RUDSTRÖM

Since Rayer 1837 gave the first description of renal vein thrombosis with infarction in childhood, this disease entity has been reported in many publications. The total number of published cases probably amounts to 300. The diagnosis has been established most frequently in necropsies. The incidence varies in big materials from 0.027–2 % (Ahvenainen & Hallman found 4 cases of renal vein thrombosis in 1958 necropsies, a frequency of 0.26 %, Campbell 45 cases among 6200, 0.7 %). Most of the reported cases of renal vein thrombosis have occurred in children suffering from serious infections. The number of "primary" cases (Sandblom) is very small. The mortality in renal vein thrombosis has earlier been estimated at more than 95 %. During the last years some cases with a good outcome have been reported. Before describing our own case of primary renal vein thrombosis which survived, a brief review of the disease will be presented.

Aetiology and Pathogenesis.—Infection and dehydration are thought to be of great importance for the development of renal thrombosis. Thus Barenberg *et al.* found at necropsy 5 cases among 25 infants who had died of epidemic diarrhoea, and renal vein thrombosis was demonstrated in the very cases that had shown the most pronounced dehydration. Renal vein thrombosis is much more common in the first months of life. The reason for this may lie in factors causing a general tendency to thrombosis. These factors are assumed to be: (1) Low arterial, capillary, and venous pressure, with a slow rate of blood-flow (Woodbury *et al.*). (2) The hydrolability of infancy, with a tendency to dehydration. (3) The comparative immobility of newborn infants, causing increased amounts of thromboplastin with resultant increase in coagulability of the blood (Waugh *et al.*) A predisposing factor for renal vein thrombosis is the anatomical nature of the renal circulation with its long capillary network causing a slowing of the blood stream. Abeshouse found that the left kidney was more commonly affected than the right, the incidence ratio being 5:3. He explains the difference by the fact that the left renal vein is longer than the right, and that it may be exposed to pressure from the aorta. Other factors suggested to favour the development of thrombosis of the renal vein include birth trauma (Sandblom).

Pathology.—The infarcted kidney is usually enlarged. Zuelzer has carried out detailed microscopical examination of 12 post-mortem specimens, and found fibrous and ischaemic infarcts in regions where the small veins were occluded by old organized thrombi, whereas the areas showing fresh haemorrhage corresponded to the distribution of newly formed thrombi. He claims that in infancy the thrombosis either is primary in the small radicles and may extend secondarily into the main branches of the renal veins, or occurs simultaneously in branches of small and large calibre. No evidence was found to indicate that retrograde extensions of thrombosis from the main stem of the renal vein played a part in the development of the process. Zuelzer is of the opinion that there is a common factor which produces either haemorrhagic infarction or renal vein thrombosis or both. This factor he claims to be stasis, the character of which, according to him, determines the degree of involvement. Gradual stasis might thus give rise to haemorrhagic infarction without thrombosis, due to anoxia to the capillary walls, with diapedesis of cells, followed by frank interstitial haemorrhage. In one of the cases reported by Mc Clelland & Hughes renal vein thrombosis with infarction was found on one side at necropsy, whereas the other kidney showed only the signs of lower nephron nephrosis.

Diagnosis.—Only in a few cases has the diagnosis been made preoperatively or during life. The differential diagnosis includes primarily malignant tumours of the kidney, haemorrhage, hydronephrosis, solitary renal cysts, and inflammatory changes in the kidneys or perirenal tissues. One of the reasons why the diagnosis is so rarely made on clinical examination is that the condition is not borne in mind, since it is not well known. Another thing which makes the diagnosis difficult is that the physical signs are often indefinite and masked behind the primary disease (Barenberg *et al.*). The urine might show only slight pathological changes. Often, however, albuminuria, haematuria, pyuria, marked oliguria, or anuria are found in connection with the palpation of a firm, smooth tumour at the site of one or both kidneys. In primary cases, renal infarction may occur a few days after birth, with shock, haematuria, and pronounced renal changes (Sandblom). To establish whether the lesion is unilateral or bilateral, Campbell & Matthews stress the value of both excretory and retrograde urography.

Prognosis and Treatment.—Renal infarction in infancy is a very serious condition. Campbell & Matthews state that over 95 % of infants will die unless promptly treated by surgery. They claim further that (1) when the lesion is unilateral, (2) the child is not hopelessly septic, and (3) when prompt nephrectomy is carried out, about 75 % may be expected to survive. This figure, given in 1942, would now probably be even higher.

In about half the cases the lesion is bilateral. In this event surgery is impossible and the outlook is always serious. Fallon, however, has reported a case of this type in which the patient survived. Abeshouse points out that extension of the thrombus to the inferior vena cava or to the opposite renal vein may develop following surgery. Nephrectomy is the accepted mode of treatment in unilateral renal vein thrombosis and infarction. Perusal of the literature reveals that only 10 cases have previously been reported in which operation was performed with success. (Campbell *et al.*, 2 cases, Sandblom, Parry, Milburn, Warren *et al.*, 2 cases, Mills *et al.*, Clark *et al.* and Smith *et al.*)

Case Report

Case history. (Pediatric Clinic, case no. 406/55). Girl, born 18/4 1955, birth-weight 3750 g, length 49 cm. Mother aged 26 years, 19-year history of diabetes mellitus. Caesarean section was performed 4 weeks before term owing tho mother's diabetes. No signs of asphyxia. Transferred same day to Pediatric Clinic for routine observation. On examination she was found to be a well-developed child, with the typical appearance of infants of diabetic mothers (much subcutaneous fat, puffiness of the face). Blood picture normal. Hb 135 %, erythrocytes 6.5 million, leukocytes 15,200. Urine normal. Prothrombin index 52. Blood sugar 48 mg %. Thrombocytes 113,000. Three days after birth obvious jaundice developed, with serum bilirubin 11.2 mg %. The jaundice increased markedly during the next few days, the serum bilirubin on 23/4 being 27 mg %. The bilirubin value subsequently fell gradually. On 26/4 the child, whose general condition had previously been good, suddenly became drowsy and vomited, and the temperature rose moderately. The urine was now found to contain protein (Esbach 4 %). Sediment: erythrocytes + + +, leukocytes +. N.P.N. normal. Abdominal palpation revealed a smooth tumour the size of an orange at the site of the left kidney. Roentgen examination of the abdomen showed a tumour with well-defined edges. Intravenous urography showed a non-functioning left kidney, and a normally-functioning right kidney. The presence of a tumour was thought not to be impossible, but bearing in mind the rapidly developing mass and the patient's comparatively unaffected general condition, the preoperative diagnosis of renal haemorrhage? perirenal haematoma? tumour? was made. During the subsequent period of observation the child's condition improved, becoming good 4 days after onset of clinical signs. The bilirubin level fell to 12.8 mg % on 27/4 and 3.8 mg % on 4/5 1955.

Left-sided nephrectomy (P. Rudström) 3 weeks after birth, on May 9th. Kidney firm, smooth, the size of an orange. Dark blood clots visible through the tense capsule. Pedicle shrunken and short, tied with double ligature. Section of the specimen showed an enlarged kidney with marked foetal lobulation. The renal parenchyma at the lower pole was necrotic and directly continous with a dark haematome somewhat larger than a hen's egg. There was evidence of infarction even at the upper pole. The middle part of the kidney appeared unaffected, and the renal pelvis and ureter were normal. There was strikingly little postoperative disturbance. Antibiotics were administered throughout, but no anticoagulants were given.

Microscopical examination on extirpated kidney. (S. Falkmer). The small and medium branches of the renal vein are thrombosed. Some of the thrombi are recent, others are undergoing organization. The branches of the renal artery are normal. Similarly, the patches of haemorrhagic necrosis are of varying age, but no organization of the infarcted areas is present. Other structures in the renal tissue and ureter are normal.

The patient was discharged 2/6 1955, and has since been seen 3 times, the most recent follow-up being on 27/1 1956. She has developed normally, and no signs of disease have been found. Urine and N.P.N. normal.

Discussion

The case reported presents the typical picture of primary renal infarction, as described by Sandblom, Campbell and others. The infant had previously been quite healthy, and the acute signs which appeared immediately before

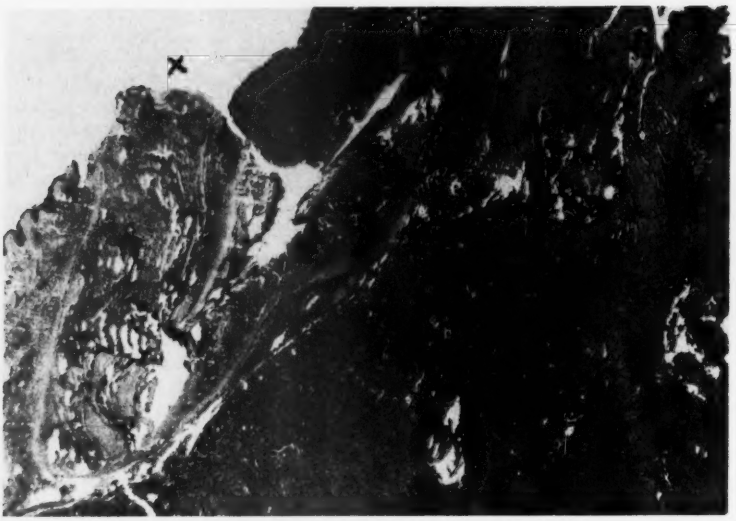

Fig. 1. Part of renal hilum with pelvic mucous membrane (above, left) and recent haemorrhagic infarct in the renal parenchyma (right). The v-shaped area (×) between the pelvic mucous membrane and the renal parenchyma consists of a longitudinal section of a medium-sized vein containing a recent thrombus. v. Gieson, × 15.

Fig. 2. Section of hilum of kidney showing a fairly small artery (above, middle, ×) without changes, a vein of similar size, immediately below, containing an old, recanalized thrombus, and (below, right, ○) part of the same vein as in Fig. 1 containing a recent thrombus. The pelvic mucous membrane (above right) and the renal parenchyma are normal. Small haemorrhages and round cells are present in the adipose tissue of the hilum. v. Gieson, × 26.

he renal tumour became palpable are clearly explained by the haemorrhage nto the kidney. We have been unable to find any support in the literature or a possible connection between the thrombosis in the child and the nother's diabetes. The infant lost rather more weight than is usual, but howed no clinical signs of dehydration. The occurrence of birth trauma was nlikely since the mother was delivered by Caesarean section. The aetiology n this case is thus unknown. Of great interest is the rapid improvement vhich set in two days after the appearance of the initial signs. It is probable hat if the child had not been under observation in hospital, the parents vould never have sought medical advice, and the diagnosis would not have een made. The haematoma might perhaps nevertheless have been resorbed nd a shrunken, fibrotic non-functioning kidney would have been the sequel f the infarction. Campbell has suggested that this may give rise to a Goldblatt mechanism with hypertension as result. One wonders whether some of he small hypoplastic kidneys often found at autopsies could occasionally e the result of renal thrombosis or infarction. Ekström is of the opinion, nowever, that such a mechanism is rarely at work.

Summary

A brief review of the literature on renal thrombosis in the newborn, from which it is found that only 10 cases successfully treated by surgery have previously been published, is followed by a case report. The cause of the thrombosis could not be demonstrated. The clinical signs were not very marked, so that the case might well have escaped recognition.

Thrombose rénale chez le nouveau-né.

Nouveau-né de sexe féminin, accouché par césarienne. Mère diabétique. Néphrectomie réalisée trois semaines après la naissance. La cause de la thrombose n'a pu être mise en évidence. Les signes cliniques étaient tout-à-fait mineurs, ce qui explique que la cause ait pu passer inaperçue. Sortie en état de guérison. 10 cas seulement traités avec succés par néphrectomie, ont été rapportés auparavant.

Nierenthrombose des Neugeborenen.

Bericht eines Falles eines weiblichen Neugeborenen, das durch Kaiserschnitt entbunden wurde und dessen Mutter Diabetes hatte. Drei Wochen nach der Geburt wurde eine Nephrektomie durchgeführt. Die Ursache der Thrombose konnte nicht nachgewiesen werden. Die Ursache kann der Beobachtung entgangen sein, da die klinischen Zeichen nicht sehr ausgeprägt waren. Das Kind wurde gesund entlassen. Es sind bisher nur 10 Fälle beschrieben worden, die erfolgreich chirurgisch behandelt wurden.

Trombosis renal en el recién nacido.

Se comunica el caso de un recién nacido de sexo femenino nacido per cesarea. Madre diabética. Nefrectomía efectuada 3 semanas después del nacimiento. La causa

de la trombosis no pudo ser demostrada pero como los signos clínicos no fueron muy marcados, ella puede haber pasado inadvertida. Dado de alta en buen estado La literatura consigna solo 10 casos tratados quirurgicamente con éxito.

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The Nature of Crystalline Material in Tissues of Lignac-Fanconi's Disease

by H. S. BAAR and STELLA BAAR

The identification of crystalline material which is found in a variety of tissues in Lignac-Fanconi's disease has apart from diagnostic value a great theoretical importance for the interpretation of the nature of the disease. Two opposed theories concerning the pathogenesis of this disorder have been presented: one assumes a renal origin, the other a prerenal metabolic one. Baar and Baar & Bickel discussed all findings which support the idea of a disorder of the intracellular metabolism of the reticulo-endothelial system which involves equally all members of this system except the littoral cells. This disorder may be due to a defect in one stage of the metabolism of sulfur-containing amino acids, e.g. the oxidation of cystine, or it may be a more generalised disorder of the formation of proteins or peptide chains which would involve a series of amino acids. Baar and Bickel favoured the latter hypothesis without being able to give conclusive evidence.

The crucial finding in Lignac-Fanconi's disease is the presence of crystals in the tissues. The hypothesis of a generalised disorder would be supported by the demonstration of crystalline material other than cystine. A series of histochemical, optical crystallographic and X-ray crystallographic methods has been applied but no evidence was found of any amino acid other than cystine crystallising in the tissues, whether the crystals seen in the sections were hexagonal plates, prisms or needles.

Recently Freudenberg, who previously (1949) supported the hypothesis of a disturbance of cystine metabolism, published a paper in favour of a general disorder of amino acid metabolism (1954). In support of this theory he claimed to have demonstrated tyrosine crystals in the bone marrow and in other tissues of Lignac-Fanconi's disease by an original method. For this purpose he coated bone marrow films or tissue sections with bovine albumin, allowed to dry, fixed with methanol and applied afterwards a solution of tyrosinase to the surface of the film. The appearance of black precipitates

he considered as proof of the presence of tyrosine. However, as source of tyrosinase he used a crude juice of mushrooms and did not attempt to identify the amorphous black precipitate as melanin. When fresh mushroom juice is allowed to stand for a few hours without any addition it becomes dark blackish-brown and a precipitate is formed similar to that described by Freudenberg. This may be due to the presence of both tyrosinase and tyrosine in the juice or may represent a "browning reaction".

We decided therefore to reexamine the problem by repeating Freudenberg's experiments with pure tyrosinase, by applying thermoanalytical methods, by supplementing the previously reported optical crystallographic investigations by the determination of refractive indices, and finally by establishing the ultraviolet absorption spectra.

(1) *Tyrosinase*

Using fresh crude juice of mushrooms a spontaneous darkening of the fluid was always seen and an abundant precipitate of black granular material when the juice was applied to fixed bovine albumin films, whether tyrosine, cystine or sections of organs of Lignac-Fanconi's disease were enclosed in the film. When the mushroom juice was diluted, using a few drops in 5 ml urine, a definite difference was seen between urines to which tyrosine was added and control urines. No such difference was seen in films and sections from Lignac-Fanconi's disease and normal controls to which mushroom juice was applied by the method described by Freudenberg. Only a very occasional granule was bleached by subsequent application of hydrogen peroxide to films with black granular material. Different results were obtained when pure tyrosinase was used instead of mushroom juice. Pure tyrosinase was obtained by a kind gift from Dr. A. L. Lane, bacteriologist of the Difco Laboratories in Detroit. This enzyme preparation is produced from potato juice by the method described by Lichtman and Sobotka. Only very scanty black granules were seen and no difference was found between films which enclosed tyrosine crystals and those which enclosed cystine crystals or sections from Lignac-Fanconi's disease or normal controls. None of the granules was bleached by hydrogen peroxide and no red precursors of melanin were seen. According to Raper the formation of melanin from tyrosine proceeds in two phases. The first is entirely enzymatic and results in the formation of a rose-coloured substance and this is followed by a non enzymatic formation of melanin. More black granules were obtained with tyrosine only when by acidification the tyrosine crystals were dissolved. With a pure enzyme preparation therefore no melanin formation was demonstrable neither in sections from various organs (lymphnodes, spleen, bone marrow) nor in bone marrow films of four cases of Lignac-Fanconi's disease. The black granules, particularly abundant with crude mushroom juice are not melanin; they may be due to a browning reaction or they may be metal sulfides.

(2) *Thermoanalysis*

We determined the melting points and the eutectic temperatures of mixtures containing as one component either cystine or tyrosine. All investigations were carried out with the original Kofler-stage[1] and most were repeated with a stage manufactured

[1] Manufactured by Reichert in Vienna.

by Gallenkamp's. The latter has the advantage of a small melting chamber which results in a smaller variation in duplicate and triplicate estimations, and in sublimation taking place only on the undersurface of the upper coverslip and not as in Kofler's stage on the "bridge" and on the covering glass plate.

The amino acids used in these estimations were all twice recrystallised and their purity checked by chromatography. The determination of melting points (M.P.) of amino acids has many pitfalls. All amino acids have a high M.P. owing to their structure. To quote Haurowitz: "That the solid amino acids also exist as dipolar ions rather than as neutral molecules is shown by their high densities and their high melting points. Both properties indicate strong electrostatic attraction between the oppositely charged ionic groups of adjacent molecules making it more difficult for them to separate than would be the case with adjacent neutral molecules." "The true melting points, if they could be determined, would probably be higher than the values reported" (Cohn and Edsall). The same structural property is probably responsible for many amino acids having instead of a sharp M.P. a melting interval which may be as much as 10°. In addition many show decomposition before melting. This explains the considerable divergence of statements in the literature. Apart from the mentioned factors, if the classical method of M.P. estimation is used and not the microscopical, a conglomeration of crystals due to their decomposition may easily be confused with real melting.

Cystine. The M.P. is according to Block and Bolling 256–258° and according to Hodgman *et al.* 258–261°. No M.P. is given in the tables of Kofler which are all obtained by the microscopical method. The following was found in own investigations: With the original Kofler-stage the highest temperature which can be obtained is a little over 350°. At this temperature all cystine crystals are decomposed being dark blackish-brown. No melting is seen and many crystals retain their shape of hexagonal plates in spite of the altered colour. We attempted to calculate the M.P. of cystine by estimation of eutectic mixtures with various substances, constructing melting diagrams and extrapolating the curve to 100 per cent cystine on the abscissa. The eutectic temperature (E.T.) can be estimated with fair accuracy although

TABLE 1

Mixture of cystine with	E.T.
Salicylic acid	120°
Phenacetin	130°
L-Cysteine hydrochloride	165°
Salophen	175°
Sedormid	182°
Saccharin	200°
Phenolphthalein	210°
Disodium salt of ethylendiaminetetracetate	230°
L-Tyrosine	250°

Kofler's "contact method" cannot be applied owing to the high M.P. of cystine and the decomposition below the M.P. The principle is that the E.T. is the lowest M.P. and that in any mixture examined under the microscope there will be an area where the proportion of the two components is that of an eutectic mixture. The lowest M.P. observed in any mixture and identical for mixtures of different proportions will be therefore the E.T. (see Kofler). In this way the E.T. can be determined when the amount of one of the components is unknown, as it is the case with tissue sections. The E.T.'s which we obtained for cystine mixtures are seen in Table 1.

However, when melting diagrams were constructed with some of the above-mentioned substances it was seen that the relevant arm of the diagram has an irregular arching which makes an accurate extrapolation impossible. The only permissible conclusion from all these experiments is that the M.P. of cystine is in the vicinity of 400°.

L-*Tyrosine* has according to Block and Bolling a M.P. of 314–318°, according to Hodgman *et al.* 295°. Kofler, however, using his microscopical method states as follows: Browning from 250° upwards. Slow melting with gas formation and browning between 260 and 270°. E.T. with salophen 184°, with diacyanamide 196°, with phenolphthaleine 245°. Our own findings were very close to those reported by Kofler, except for the E.T. with phenolphthalein: M.P. 260–270°. E.T. with sedormid 179°, with salophen 180°, with saccharin 200° and with phenolphthalein 215°.

For examination of crystals in tissues paraffin sections were prepared from alcohol-fixed material, mounted on half of a slide of the standard size, deparaffinised without being taken down to water, dried and pulverised first with the help of a Hagedorn needle and then by rotating the coverslip on the slide. In the powder crystals were easily recognisable. Their M.P. was estimated and mixtures prepared with most of the above-mentioned crystalline substances of known M.P.'s. When no addition was made to the crystalline material present in the sections all crystals remained unmelted at the temperature just above 350°, in other words they behaved as did crystals of pure cystine. The E.P.'s with several substances were identical with or close to those of the corresponding cystine mixtures, e.g. with salicylic acid 120°, with sedormid 180°, with phenolphthalein 210°. However, the E.T.'s of cystine and of tyrosine with the examined substances are either identical or in view of the difficulties in the determination too close together to yield reliable results in examination of crystals in tissue sections. A clear-cut result was on the other hand obtained when L-tyrosine was added to pulverised tissue sections. L-Tyrosine mixed with L-cystine produces a considerable depression of the M.P. with an E.T. of 250°. *The same depression of the M.P. was obtained when even a small amount of* L-*tyrosine*

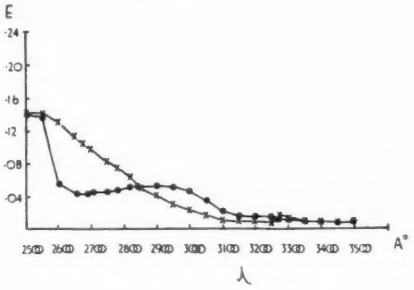

Fig. 1. Ultraviolet spectra of: —
· — · — · — · — L-Tyrosine.
x—x—x—x— L-Cystine.

was added to pulverised sections of lymph nodes, spleen or bone marrow of Lignac-Fanconi's disease.

(3) ***Refractive Indices***

L-Cystine crystallises as monoaxial crystals of the hexagonal system with a negative optical sign of anisotropy. The refractive indices are according to Keenan: $n_\omega = 1.700$, $n_\varepsilon = 1.640$. Important for the diagnosis is the highest refractive index. It has to be born in mind that ideal hexagonal plates, i.e. such with parallel faces of basal sections are isotropic because the light passing the main crystalline axis is not divided into an ordinary and an extraordinary ray. The determination of n_ω shown by such crystals has therefore to be made in non polarised light as it is done with isotropic crystals. When immersed in a mixture of α-monochloronaphthalene and methylene iodide with $n_D = 1.700$ all hexagonal plates and prisms disappeared as well in pure cystine as in crystals of tissues from Lignac-Fanconi's disease. L-Tyrosine forms biaxial crystals with $n_\alpha = 1.550$, $n_\beta = 1.600$ and $n_\gamma^9 = 1.680$. Of greatest diagnostic value is the determination of n_γ, as this allows exactly to identify a single needle as tyrosine or to exclude this diagnosis. When L-tyrosine needles are mounted in a liquid of $n_D = 1.680$ all needles disappear completely when their longest dimension lies parallel to the vibration plane of the polariser. The preparation is placed on the stage of a polarising microscope with crossed Nicols, the stage is rotated until the observed needle disappears and the analyser is then removed (see Hartshorne and Stuart). A tyrosine needle will then invariably remain invisible to reappear only with a slight rotation of the stage.

This was first checked on needles of pure tyrosine and then the same method applied to sections of bone marrow, lymph nodes and spleen from four cases of Lignac-Fanconi's disease. A great number of slender prisms and needles was examined in this way and in every instance the crystal reappeared when the analyser was removed. Both, this finding and the depression of the M.P. by addition of tyrosine, are *unequivocal evidence of the absence of tyrosine crystals in the tissues of Lignac-Fanconi's disease.*

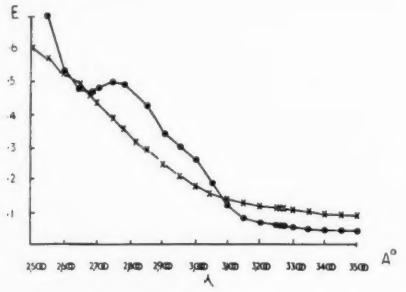

Fig. 2. Ultraviolet spectra of: — x—x—x—x— Extract from spleen of Lignac-Fanconi's disease. .—.—.—.—. Spleen extract to which L-tyrosine had been added.

(4) *Ultraviolet Spectra*

Pure L-cystine and L-tyrosine were dissolved in dilute ammonia of pH = 11.0. Ultraviolet absorption spectra were determined with the help of the Unicam spectrophotometer. The absorption curves are seen in Fig. 1. Tyrosine shows a gentle but marked elevation between 2750 Å and 3000 Å, while in the absorption curve of cystine only a minimal elevation is seen between 3260 Å and 3300 Å.

Alcohol-fixed spleens from three cases of Lignac-Fanconi's disease were dried, pulverised and extracted with dilute ammonia of the same pH. Fig. 2 shows the ultraviolet absorption spectra of one such extract and of another one to which a trace of L-tyrosine had been added. Although the tyrosine elevation in tissue extract to which tyrosine had been added is not identical with that of a solution of pure tyrosine, it is clearly seen in that extract and absent in the original one. There is a lower limit for tyrosine concentration to be detectable in the ultraviolet absorption curve. The finding has therefore only corroborative value but cannot be considered as unequivocal evidence for the absence of tyrosine crystals as are the results listed under (2) and (3).

From all these findings it may be concluded that tyrosine *does not crystallise* in tissues of Lignac-Fanconi's disease. The needles observed in such tissues are unusual habits of cystine crystals. It has been shown by Baar and Bickel that such a habit can be regularly reproduced when pure cystine is recrystallised from an agar solution.

We wish to thank Dr. J. P. Bull, Director of the Medical Research Council Industrial Injuries and Burns Unit, for the laboratory facilities for a part of these investigations, Mr. A. R. Detheridge for technical help, and Mr. J. G. Williamson for photographic work.

Summary

The nature of crystals in tissues of Lignac-Fanconi's disease has been investigated with the help of pure tyrosinase, by thermoanalysis, by determination of refractive indices and by the ultraviolet spectra. It was conclusively shown that tyrosine crystals were absent in all examined sections. Our findings are consistent with the crystals consisting only of L-cystine.

La nature du matériel cristallin contenu dans les tissus de la maladie de Lignac-Fanconi.

La nature des cristaux dans les tissus de la maladie de Lignac-Fanconi a été examinée avec l'aide de la tyrosinase pure, par la thermoanalyse, par la détermination des index réfractaires et par des spectrogrammes ultraviolets. On a démontré avec certitude que les cristaux de tyrosine étaient absents dans toutes les coupes examinées. Nos resultats sont en bon agrément avec la consistence des cristaux de la L-cystine seule.

Die Beschaffenheit des kristallinen Materials im Gewebe bei Morbus Lignac-Fanconi.

Die Natur der kristallinen Substanzen im Gewebe bei Morbus Lignac-Fanconi ist mit Hilfe von reiner Tyrosinase, durch Thermoanalyse, durch Bestimmung der refraktären Indices und durch ultraviolette Spektren untersucht worden. Es wurde endgültig gezeigt, dass in allen untersuchten Abschnitten Tyrosinkristalle abwesend waren. Unsere Befunde lassen sich mit der Beschaffenheit der Kristalle aus reinem L-Cystin vereinbaren.

Naturaleza de la sustancia cristalina hallada en los tejidos en la enfermedad de Lignac-Fanconi.

Por medio de la tirosinasa pura, termoanálisis, determinación del índice de refracción y espectro ultravioleta, se estudió la naturaleza de los cristales hallados en los tejidos de pacientes con enfermedad de Lignac-Fanconi. No se encontraron cristales de tirosina en los cortes examinados, hallándose solamente cristales de L-cistina.

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Albright's Syndrome

A Brief Survey and Report of a Case in a Seven-Year-Old Girl

by ULLA ARLIEN-SØBORG and TORBEN IVERSEN

In 1936, Albright, Butler, Hampton and Smith (1) presented five cases of a syndrome with multiple localized bone changes, areas of abnormal pigmentation of the skin, endocrine dysfunction and, in females, precocious puberty. Single cases had previously been reported, first by Weil (20), who in 1922 presented a 9-year-old girl who since the age of 18 months had had periodical vaginal bleeding and had sustained eight spontaneous fractures. The skin was abnormally pigmented and the bone age advanced. The roentgenographic appearance of the bones was interpreted as an unusual form of osteopsathyrosis. Among other cases reported in the literature the one described by McCune (15, 16) is noteworthy. The complex of signs cited is now generally referred to as Albright's syndrome. In 1938, Lichtenstein (12) showed that multiple bone lesions similar to those seen in Albright's syndrome may occur as an isolated phenomenon, and the osseous anomaly was termed "polyostotic fibrous dysplasia". As it was later demonstrated that the osseous changes may be confined to one bone, the name was changed to "fibrous dysplasia of bone" (13).

The aetiology of Albright's syndrome is unknown. There is no definite evidence suggesting that the condition is hereditary. Albright *et al.* (1) suggested it to be due to a neurological disturbance or an embryological defect. No specific therapy is available.

While cases of polyostotic or monostotic fibrous dysplasia are relatively frequent, the fully developed Albright's syndrome is rare. By a search of the literature up to 1949, Pritchard (18) found reports of 256 cases of fibrous dysplasia, of which 181 were polyostotic. Among the patients with polyostotic changes, 79 had abnormal pigmentation of the skin, while 37 out of 82 females and 5 out of 83 males exhibited precocious puberty. Up to 1956, at most 100 cases of Albright's syndrome in its complete form have been reported; the vast majority of these cases occurred in females.

From Scandinavia, Albright's syndrome in a child has only been described by Hernberg and Edgren (8). However, the patient, a 14-year-old girl, did

not exhibit signs of sexual precocity. On the other hand, several Scandinavian authors have reported cases of fibrous dysplasia of bone in children and adults (9, 10, 14, 19, 21, and others).

A brief survey of Albright's syndrome is given below followed by the report of a case in a 7-year-old Danish girl.

Clinical Manifestations

The osseous changes may be asymptomatic and may be accidentally revealed at a roentgen examination, or they may give rise to pain, limping, spontaneous fractures or deformities, especially outward bowing of the upper end of the femur, which may result in the so-called shepherd-crook deformity. In one case (15, 16), incipient bowing of the lower extremities was observed as early as at the age of about one year, and during the following year the deformity became so pronounced that walking was rendered difficult. The changes in the base of the skull may result in facial asymmetry, protrusion of the eye and visual disturbances. In adult life the osseous changes become stationary.

The pigmentations appear as café-au-lait-coloured non-elevated patches with well-defined, very irregular contours. They may be confined to one small area or be scattered over large areas, particularly involving the back, buttocks, thighs or, more infrequently, the face and neck. The cutaneous changes are usually most conspicuous on the side where the osseous changes are most pronounced. In rare cases, pigmentation of the mucous membranes of the mouth is observed. The pigmentations most frequently develop at the age from 4 months to 2 years, but they have also been observed as early as during the first few weeks of life (2). In most cases, the pigmented areas do not spread.

Precocious puberty.—In about one half of the girls the menarche occurs at the age of 1–5 years and in about one third at the age of 6–10 years (3). Vaginal bleeding has been observed as early as on the second day of life (7) and at the age of 4 months (1, 6). The bleeding usually persists for 2–4 days and may occasionally be profuse. It may be regular or irregular, occurring at intervals of weeks or months. Development of the breasts and appearance of pubic and axillary hair usually begin later than the menarche, most frequently between the ages of 5 and 10 years, but have been observed at about 2 years (15, 16); hypertrophy of the external genitalia has been encountered at the age of 6 months (1).

One case of Albright's syndrome with pigmentations and sexual precocity, but without bone lesions is on record (11). This condition has later been termed polyostotic fibrous dysplasia sine fibrous dysplasia.

As already stated, precocious puberty has been observed in boys only in a few cases.

Other endocrine features.—Rapid skeletal development with premature epiphyseal union is often seen in both sexes, resulting in accelerated growth in childhood and short physical stature in adult life.

In addition to precocious puberty, hyperthyroidism has been described in a number of cases, and adiposogenital dystrophy (4), acromegaly (5) and insulin-resistant diabetes mellitus (17) have also been observed.

Laboratory Findings

It is usually stated that the serum calcium and serum phosphorus concentrations are normal. However, a review of the literature (3) showed that the calcium concentration was elevated (to over 12 mg per 100 ml) at least temporarily in 20 per cent and the phosphorus concentration diminished (in children to below 3.5 mg per 100 ml) in about 40 per cent of the patients with polyostotic fibrous dysplasia. The concentration of alkaline phosphatase is most frequently increased, but may be normal. The cholesterol concentration is normal. Urinary calcium excretion is usually normal, but may be increased. The excretion of gonadotrophins, oestrogens and 17-ketosteroids in the urine is not increased.

Bone Lesions

Roentgenographic appearance.—All bones may be involved, the sites of predilection being the long bones. The multifocal changes are bilateral in about one half of the cases and left-sided in three fifths and right-sided in two fifths of the remaining cases (3). The femur is most commonly involved and then, in the order of decreasing frequency, the tibia-fibula, pelvis, humerus, and radius-ulna (5). If the base of the skull is affected, the skeletal changes of the extremities are usually bilateral. The process is localized to the diaphysis and metaphysis of the bone, while the epiphyses are usually not involved. The changes may spread by erosion of the cortex, which may be reduced to a thin layer, and may extend to the periosteum. Expansion of the entire diaphysis may be seen. The bones involved may be longer than normal. It is a characteristic feature that the non-affected areas of bone tissue show normal structure and calcification.

In the central parts of the affected bone are often found more or less circumscribed cystlike areas of lessened density, which are either sharply defined or gradually vanish in the surrounding tissue. Due to the presence of trabeculae, the cystlike areas often assume the appearance of 'broken

glass', but they may also be more blurred in appearance, suggestive of 'ground glass'. Longitudinal bands of decreased density may occasionally be observed. In addition, dense bone tissue may be seen, possibly in the form of sharply demarcated endosteal areas of increased density which may obliterate the marrow cavity.

The anterior and medial parts of the base of the skull and the maxilla may reveal specific changes, manifested by deposits of dense sclerotic bone tissue, especially in the region of the sella turcica. The orbital roof may be thickened, and the nasal sinuses obliterated on one or both sides.

Pathology.—The pathological process begins in the medullary cavity as a fibrous proliferation of the connective tissue extending to and replacing the adjacent bony tissue. The connective tissue is relatively firm, waxlike or rubber-like, and of a yellowish white or reddish brown colour; sometimes it contains cystlike cavities filled with fluid.

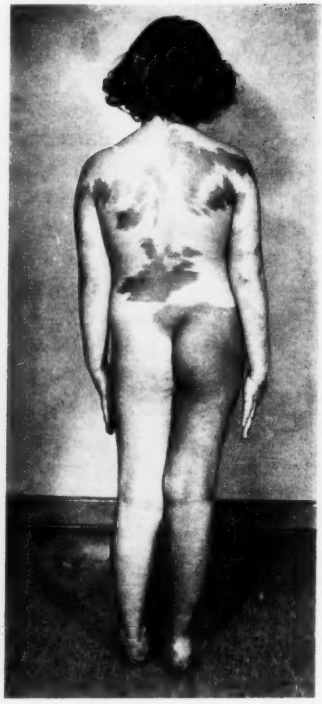
Histologically, the pathological tissue may be abundant in smaller or larger spindle-shaped cells in a finely fibrillary stroma, or it may be poor in cells and made up of a markedly collagenous stroma arranged in whorls and bundles. The vascularity is usually poor. Oedematous areas and cysts with a clear or bloody content may be seen. Scattered in the connective tissue there may be partially calcified bone trabeculae, often surrounded by osteoblasts. In addition, there may be islands of cartilage with calcifications in the periphery. The stroma may contain lymphocytes, groups of giant cells and, on rare occasions, foam cells. Surrounding bony fragments and islands of cartilage, osteoclasts may be present. The osseous and cartilagineous tissues are believed to have arisen by metaplasia of the connective tissue.

Case Report

The patient was a girl, aged 7 years, born in 1948.

Past history.—The maternal uncle of the patient's father and the patient's maternal grandmother had diabetes mellitus. The parents were in good health. There were no known cases of abnormal pigmentation, precocious puberty or bone disorders in the family. The patient was the third of a sibship of four. The patient's siblings, all boys, were healthy. The pregnancy and delivery had been normal; birth weight 4380 g, length 53 cm.

When the infant was one week old, the mother noticed a faint brownish discolouration in the lumbar region, and at the age of 2–3 weeks distinct patches had developed. On the eighth day of life vaginal bleeding appeared and lasted for 4 days. Since then, vaginal bleeding had appeared at the age of 6 months, lasting one day, and at the age of 5½ years, lasting four days. At 5 years, pain, enlargement and tenderness of the breasts developed, lasting for about a fortnight. These reactions were not accompanied by vaginal bleeding. Pain, limping and fractures had never occurred. Since infancy the patient had suffered from pyuria at intervals of a few months, and enuresis had been present. Otherwise the patient was well.



Figs. 1 and 2. Patient at the age of 8 years. Large café-au-lait-coloured pigmentations with irregular contours. The right lower extremity is longer than the left.

The patient was admitted to this hospital in February 1955 for closer investigation because of the recurring pyuria.

Physical examination.—The appearance of the patient corresponded to her age. She was slightly obese (height 121 cm, weight 26.5 kg). The right leg was 3 cm longer than its fellow. Several large light brown patches with irregular contours were seen on the left cheek, the back, lumbar region, the right gluteal region, both upper arms, right forearm and right lower extremity (Figs. 1 and 2). The mucous membranes of the mouth did not show any pigmentation.

The breasts were not enlarged; the external genitalia were normal, and there was no pubic and axillary hair. No further abnormalities were disclosed at the physical examination. Ophthalmological and neurological examinations showed no abnormal findings. Mentally, the patient was slightly retarded.

Laboratory findings.—Haemoglobin 15.5 g per 100 ml. Serum calcium 9.7–9.3 mg and serum phosphorus 5.0–3.3 mg per 100 ml; alkaline phosphatase 21–21 Buch units (normal for age 7–10 units); serum albumin 5.0 g and serum globulin 2.2 g per 100 ml; electrophoretic analysis of the serum showed a normal pattern; serum cholesterol 152 mg per 100 ml; fasting blood sugar 98 mg per 100 ml; glucose-tolerance test normal.

Fig. 3. Roentgenogram of skull showing sclerosis of the anterior and middle cranial fossae.

The urine did not contain albumin or sugar; microscopic examination showed numerous leukocytes. Urinary hormone excretion in 24 hours: gonadotrophins below 50 M.U. (not demonstrated), oestrogens below 20 M.U. (not demonstrated), androgenic hormones 1 I.U., 17-ketosteroids 0.8–1.1 mg, corticoids 0.35 mg. Following three days of a diet low in calcium, the urinary calcium excretion on three consecutive days was 35, 15 and 14 mg in 24 hours. B.M.R. –9 per cent.

Roentgen examination of the skeletal system.—The *skull* showed a dense pattern of bone in the anterior and middle cranial fossae (Fig. 3). The right maxillary sinus was almost completely obliterated by sclerosed bone tissue, and the ethmoidal sinus could not be made out. Both lesser wings of the sphenoid were large and plump. The sella turcica was of normal size. Almost all the *extremital bones* were affected, particularly on the right side. The unaffected areas of the bones showed normal structure and calcification. The development of the epiphyseal lines and centres of ossification corresponded to the chronological age. The right humerus showed endosteal densities on the inside of the cortex of the shaft (Fig. 4). The spongiosa of the right radius and ulna

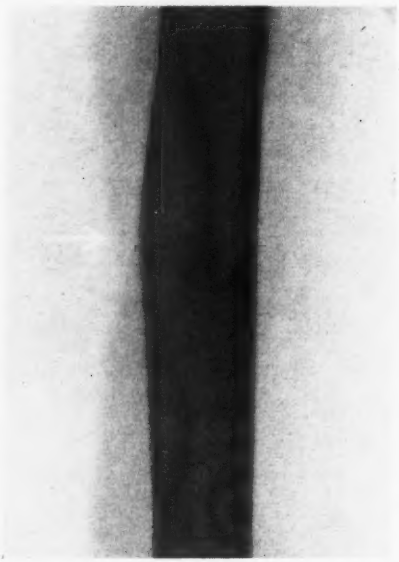


Fig. 4. Endosteal densities on the inside of the right humerus.

revealed longitudinal bands of lessened density. The neck of the right radius was slightly expanded. The right femur was about 2 cm longer than its fellow. The neck of the right femur was somewhat plump; the spongiosa revealed some ill-defined areas of lessened density (Fig. 5). Distinct endosteal densities were seen on the cortex of the femoral shaft. The right tibia and fibula showed changes similar to those observed in the femur. The metacarpal and metatarsal bones revealed cystlike areas of lessened density, which were very distinct in the first and fifth right metacarpal and the fifth left metacarpal bones (Fig. 6). No changes were present in the thorax or the thoracic and lumbar vertebrae.

Urography showed normal conditions.

Histological examination of a biopsy specimen from a cyst wall in the fifth left metacarpal bone showed, in sections of decalcified tissue, a finely fibrillary connective tissue with many cells having small, dense, elongated nuclei. The connective tissue contained bone trabeculae without a distinct lamellar structure. There was no sharp demarcation between the bone trabeculae and the finely fibrillary connective tissue. Inflammatory infiltrations were absent (Fig. 7). Histological diagnosis: Fibrous dysplasia of bone (Dr. Tage Lund).

Course.—The urinary-tract infection subsided after treatment with antibiotics, and the patient was discharged after a month in hospital. In October 1955, the girl was swept off her feet while playing and sustained a short oblique fracture of the right tibia and fibula about 10 cm below the knee joint. She was admitted to the Department of Surgery of this hospital, where normal union in anatomical position occurred.

Fig. 5. Neck and proximal part of the shaft of the right femur showing slight expansion and cystlike areas of lessened density.

Fig. 6. Right fifth metacarpal with cystlike areas containing trabeculae suggestive of "broken glass".

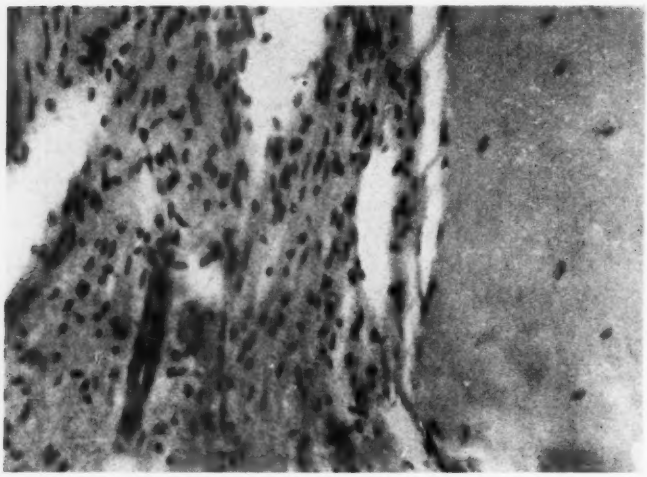


Fig. 7. Photomicrograph of pathological tissue from the left fifth metacarpal bone. Fine fibrillary connective tissue with numerous cells. To the right bone tissue without distinct lamellar structure.

Conclusions

The case of Albright's syndrome described in this paper did not present any diagnostic difficulties. The pigmentations, roentgenographic changes and histological picture were typical. Vaginal bleeding appeared for the first time at the age of one week and on two subsequent occasions. Growth of pubic hair and enlargement of the breasts have not yet occurred.

Summary

Following a brief survey of Albright's syndrome, a case in a 7-year-old girl is reported. The patient had had café-au-lait-coloured pigmentations since the first weeks of life. Vaginal bleeding lasting up to four days occurred at the ages of 7 days, 6 months and 5 years. Pubic hair and enlargement of the breasts were absent. Roentgenograms revealed typical changes in the base of the skull and the extremital bones, particularly on the right side. Histologically, the affected bone tissue showed signs of fibrous dysplasia of bone.

Le syndrome d'Albright.

Une courte revue du syndrome d'Albright est donnée et un cas d'une jeune fille de sept ans est rapporté. La patiente a présenté une pigmentation de café-au-lait depuis les premières semaines de sa vie. Des pertes de sang vaginales qui duraient jusqu'à quatre jours étaient constatées à l'âge de 7 jours, 6 mois et 5 ans. On ne observait pas

le poils pubiens ou d'agrandissement des mamelles. Les radiographies montraient des hangements typiques dans la base du crâne et dans les os des extrémités, particulièrement du côté droit. Les coupes histologiques des os affligés montraient des signes de ysplasie fibreuse.

lbright-Syndrom.

Es wird ein kurzer Überblick über das Albright-Syndrom gegeben und von einem all eines 7jährigen Mädchens berichtet. Der Patient hatte seit den ersten Lebenswochen café-au-lait-gefärbte Pigmentierungen. Im Alter von 7 Tagen, 6 Monaten nd 5 Jahren traten Vaginalblutungen auf, die bis zu vier Tagen anhielten. Schambeaarung und Vergrösserung der Brustdrüsen waren nicht vorhanden. Röntgenuntersuchungen zeigten typische Veränderungen an der Schädelbasis und den Extremitäten, nsbesondere der rechten Seite. Histologisch fanden sich Zeichen von fibröser Dysplasie er befallenen Knochen.

Sindrome de Albright.

Se hace un breve resumen del sindrome de Albright presentándose el caso de una iña de 7 años. Esta mostró una pigmentación café con leche desde la primera semana le vida. Hemorragias vaginales de hasta 4 días de duración ocurrieron a las edades le 7 dias, 6 meses y 5 años. No presentó pelo pubiano ni aumento de tamaño mamario. Las radiografías revelaron típicos cambios en la base del cráneo y huesos de las extremidades, particularmente en el lado derecho. Histologicamente el tejido afectado mostró signos de displasia fibrosa ósea.

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Cat as a Possible Source of Infection in a Case of Congenital Toxoplasmosis

by POUL H.F. BORGEN, STIAN ERICHSEN and BRYNJULV STANDAL

It seems to be generally accepted that human toxoplasmosis is transmitted from animals. Infection from man to man has not yet been conclusively demonstrated except in the special case of toxoplasmosis congenita. The infection has been shown to occur in practically all domestic animals and in several wild mammals, especially rodents (Hülphers, Lillengen & Rubarth, and Christiansen & Siim) and birds. In this country toxoplasmosis in chickens (Erichsen & Harboe) and in dogs (Erichsen & Sandbu) has been described. Several modes of transmission have been considered: droplet infection, various possibilities of contact, bites of bloodsucking arthropodes, infection by the gastro-intestinal route—but it is not known which one is the most important.

Toxoplasma gondii has been demonstrated in edible portions of beef carcasses, colostrum (Sanger, Chamberlain, Chamberlain, Cole & Farrell), milk (Chamberlain, Docton & Cole), blood, lymph nodes, saliva, secretions from the nose and conjunctivae, urine and feces.

Particular interest has been attached to dogs and cats as possible sources of infection because these animals often live in quite close contact to their owners (Westphal & Finke). Beverley, Beattie & Roseman examined the sera from veterinary surgeons, abattoir workers, rabbit contacts and rabbit trappers and found significantly higher dye-test titers than normal. This investigation indicated a relatively high frequency of past inapparent infections in persons who had had repeated contacts with animals, and especially with rabbits.

With regard to clinical manifestations of human toxoplasmosis several reports have been published where the authors suppose that a particular animal has been the source of infection. However, the interpretation of these reports is rendered difficult, chiefly because the diagnosis with regard

to the animal often seems to be based on a single serologic observation without any demonstration of the parasite. We cannot be sure that the low dye-test titers in the range from $\frac{1}{4}$ to $\frac{1}{64}$, such as often are found in dogs and cats (Miller & Feldman), really mean that the animals in question are toxoplasma carriers. Another question arises concerning the specificity of the dye-test (Awad).

Therefore the cases of most interest are those where it has been possible to prove the diagnosis on both sides in a particular contact between man and animal, either by demonstration of the parasite, or by the presence of well-known clinical manifestations confirmed by a typical serologic response. However, reports that fulfill these conditions are rather scanty. The most instructive in this respect seem to be the examinations by Cole, Prior, Docton, Chamberlain & Saslaw of "pet dogs" and their human contacts. Barnett, Lebhar & Longworth's report from Connecticut should also be mentioned. In this case it was possible to demonstrate "small granulomas" in the heart and brain of a cat that had been in contact with a woman who gave birth to a child with toxoplasmosis congenita. Siim reports that one of his cases with acquired toxoplasmosis (benign lymphadenitis) had played with a cat that showed a dye-test titer 1/100. The animal died, and unfortunately no further examinations could be performed.

Recently we had the opportunity to examine a case of toxoplasmosis congenita in a 3-month old child where the diagnosis chronic toxoplasmosis or "toxoplasma-carrier state" could be proved in a cat living in household contact with the mother of the patient. This case-report also illustrates the necessity of good cooperation between the physician in charge of the case, the toxoplasma diagnostic service and the veterinary pathologist.

Case Report

The patient (L. H.), a female full-term infant born April 30, 1955, was admitted to Fylkessjukehuset i Molde, Eye Dept., August 9, 1955, because of pronounced nystagmus.

Her family consisted of the father (A. H.) born September 23, 1923, and a sister (E.A.H.) born September 22, 1950, both in good health. Neither of them had any anamnestic or clinical symptoms that could be associated with toxoplasmosis. The mother (P.H.) born September 29, 1922 contracted tbc. pulm. 1945 and was treated with pneumothorax for a few years from 1947 on. Lobectomia pulm. sin, was performed 1952 at Rikshospitalet, Kir. avd. A, Oslo, otherwise she had been healthy. She felt quite well throughout the pregnancy and did not suffer from any febrile illness during that time. Nor did she notice any glandular enlargement or eye-symptoms. Delivery (at Fylkessjukehuset i Molde) was without complications. Child: Birth weight 3250 g. Length: 50 cm.

P. H. stayed at home the whole time during the pregnancy. The family H. owns a little farm. Their domestic stock consisted of 7 cows, 4 sheep, 3 cats and fowls. They

had no dogs. The wife had been looking after the animals while the husband was employed outside the household.

One of the cats got sick and was ailing a few weeks. This special cat was troublesome in that it would sleep in the beds of the family and often jumped up on the dining-table and filched food. At last it was shot and the body disposed of. At this time the pregnancy was of 5 months duration. The two remaining cats—dam and brother—of the cat that was shot, seemed to be in excellent health the whole time. They usually got their food in the sheep-cot and their foodbowls were cleaned there. These cats were later on sent alive to Oslo for examination (see below). Even though it was possible to demonstrate toxoplasma pseudocysts in the brain of one of them, it seems reasonable to assume that it was just the above-mentioned sick cat that was the real source of infection in this case. With regard to the cows and sheep, only serological examination was performed. From the fowls no sera were available, but the brain and eyes from two hens, taken at random in the flock, were examined histologically. Neither cows, sheep nor fowls had shown any symptoms of illness during the critical time.

Immediately after delivery the child was transferred to "Symra"—a home for children exposed to tuberculosis. During her stay here, she increased normally in weight. Nothing abnormal could be seen until she was 2 months old when the above-mentioned abnormalities became visible.

Present status August 9, 1955.

Physical condition average. The child seemed to be apathetic in some ways. The head was larger than the average, with a circumference of 43 cm (average 40 cm) with prominent tubera parietalia. The anterior fontanel was somewhat large, but did not show increased tension. Otherwise no abnormalities could be detected (eye-examination: see below). The liver, the spleen and the superficial lymph nodes were not enlarged. Neurological examination revealed no abnormalities. Ophtalmologic examination: Horizontal nystagmus and complete loss of fixation. Anterior parts of the eyes: normal. The pupils were round, equal, 3 mm, light-reactive. The lenses were clear. Both corpora vitrei showed pronounced turbidities with small floating opacities. The fundi oculi could be seen with difficulty on both sides, and one could catch a glimpse of a great grayish infiltration in the central part of both fundi. Diagnosis: Bilateral chorioretinitis in an active phase.

X-ray caput: symmetric, fine, streak-shaped calcifications in the hemispheres. The suturae cranii were not wider than normal.

X-ray thorax: normal.

Spinal fluid showed somewhat increased protein content. Pandy: + + +, Heller: + 1/30, − 1/40. Cells: 1/3.

WR neg. in blood and spinal fluid. No growth of TB from spinal fluid. Rectal temp.: 37°C. Pulse: 120/min.

W. bl. c. count: 8300/mm^3. Hgb.: 90 %. Blood sedimentation rate: 3 mm. Blood differential count: Band neutrophile metamyelocytes: 11 %, polymorph.: 14 %, large lymphocytes: 58 %, small lymphocytes: 2 %, monocytes: 8 %, a few plasma cells, unclassified cells: 7 %. General impression: infectious blood picture. The major portion of the cells were mononucleated, ungranulated (Chief Physician Helland Hansen). Specific serologic data concerning the patient and her family: see below.

With regard to the mother (P. H.): complete general examination: normal findings (cicatrice after operation). Ophtalmologic examination: normal. W. bl. c. count: 8900/mm^3. Hgb.: 95 %. Blood sedimentation rate: 11 mm. Temp.: 37°C. WR (blood):

Fig. 1. Toxoplasma. Pseudocyst in mid-brain of the female cat. × 1500.

neg. Blood diff. count: eosinophils: 3 %, polymorphs: 48 %, large lymphocytes: 12 %, small lymphocytes: 30 %, monocytes: 6 %. Normal types of cells.

The child (L. H.) immediately got sulfadiazine (4 g) and aureomycin (2.8 g) with a daily dose of 0.4 g each. Shortly after this treatment her corpora vitrei cleared up. However, her dye-test titer did not decrease and 6 weeks later the treatment was repeated with the same drugs, 2.4 g of each. The improvement of her eye-symptoms continued and after 3 months stay at the hospital she could be discharged. At this time her general condition had improved considerably and she could sit without support. The birth weight had been doubled at an age of 6 months.

Ophthalmologic examination at discharge: Some fixation ability was now present. She followed light with the eyes. Right corpus vitreum was quite clear. A chorioretinitic focus was visible below and on the temporal side of macula. Its size corresponded to 4–5 papillary diameters and the boundaries were sharp with large deposits of pigment in the margins. The whole process seemed to have acquiesced. Left corpus vitreum still showed some turbidities. The chorioretinitic focus in this eye had the same size and localization as on the right side, but the infiltration was more grayish and with diffuse boundaries. This focus still gave the effect of some activity.

However, the patients improvement was only temporary. January 18, 1956, she was again admitted to the hospital in a very poor general condition. A marked hydrocephalus had developed and there was also a flare-up of the chorio-retinitis.

Specific serologic data concerning the family H.:

Technique used: Kåss (1954). The dye test values reported are the final serum dilutions after 1 part of antigen and 2 parts of accessory factor have been added.

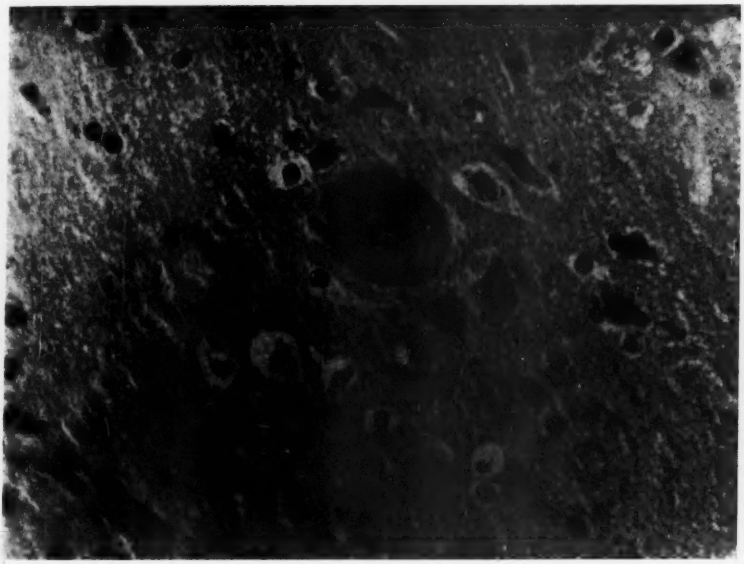

Fig. 2. The same pseudocyst as shown in Fig. 1. × 640. Note the reactionless tissue surrounding the pseudocyst.

The designation: ± is used when 40 to 60 % of the toxoplasma organisms are unstained. Complement fixation tests (c.f.t.) were performed on sera from the separate dates in the same test run. No sera were anticomplementary.

A. H. (father) and E. A. H. (sister), September 20, 1955: Dye test: − 1/4 and c.f.t.: − (undiluted).

L. H. (patient): Blood was taken on the following dates: August 22, August 30, October 22, December 1, 1955 and January 18, 1956. The same dye test titer + 1/3200 was found in all these serum samples, except for December 1, when a drop to + 1/1600 was noted. The c.f.t. titer ran a quite parallel course. The corresponding values were + 1/320, + 1/320, + 1/320, + 1/160 and + 1/320. Inoculation experiments on white mice with whole blood from the patient were performed September 26, 1955. The result was negative.

P. H. (mother): Dye test, September 10, + 1/1000; October 22, + 1/800 ± 1/1600; December 1,1955, + 1/160; January 18, 1956, + 1/160. C.f.t.: September 10, + 1/80; December 1, + 1/20.

Post-mortem Findings in the Cats

The two remaining cats, the female and the young male (son) were sent to the Department of Pathological Anatomy, Veterinary College of Norway, for post-mortem examination. Both were in excellent condition on arrival (September 22, 1955).

The animals were anaesthetized with ether and blood samples for serological examination were collected from their jugular veins. They were put to death with con-

tinued application of ether. The autopsies, which were performed immediately afte euthanasia, were completely negative. Material for inoculation experiments wer taken from both brains (medulla, occipital pole of hemispheres). Specimens for histo logical examination were collected from the liver, kidneys, pancreas, intestinal lympl glands, heart, lungs, muscles (psoas) and brain (medulla, mid-brain, basal ganglia cortex, cerebellum) of both cats. The specimens were embedded in paraffin, sectione at 5 microns and stained with hematoxylin-eosin. Neither of the cats revealed histolog ical changes in organs other than the brain.

In the brain of the female, two submiliary foci were found, one in the mid-brain an one in the cortex. Each focus consisted of a central necrotic area surrounded by micro glial cells, lymphoids and a few macrophage-like cells containing granular brown pig ment in their cytoplasm. Microorganisms could not be seen in these sections. Approxi mately forty serial sections were then taken from each of the 5 brain specimens. Twenty of these serial sections from each part of the brain were stained and examined systematically. This examination of a total of one hundred sections revealed thre different pseudocysts, 2 in the mid-brain and 1 in the cerebellum, which were typically spherical and could easily be stained by the periodic acid—Schiff method. The cerebral tissue surrounding the pseudocysts showed no signs of reaction (Fig. 2.). The brain of the male cat was examined in the same way, but neither lesions nor pseudocysts were found.

Inoculation experiments were performed with the brains from both cats by intra-peritoneal and intracerebral injection into white mice. These attempts and further sub-passage experiments too were completely negative.

Serological examinations of the animals, September 22, 1955. (Same technique as above.)

Female cat:	Dye test: + 1/200	Complement fixation test: + 1/32
Male cat:	Dye test: + 1/10 , ± 1/40	Complement fixation test: −

No sera were anticomplementary.

Sheep No.	Dye test
1	+ 1/10, ± 1/40
2	± 1/4 , − 1/10
3	+ 1/40, − 1/80
4	+ 1/10, ± 1/40

(The sera from two sheep kept at Kaptein W. Wilhelmsen og Frues Bakteriologiske Institutt, Rikshospitalet, showed the following dye test values: + 1/10 and − (+) 1/4 when the same technique was used. The animals have always been in good health.)

Cow No.	Dye test
1	± 1/4 − 1/10
2	+ 1/10 ± 1/40
3, 4, 5, 6 & 7	− 1/4.

The interpretation of the low dye test values found in the sheep and two of the cows is difficult, as emphasized above.

Histological examination of the brains and eyes of two hens showed an entirely normal picture.

Summary

Possible toxoplasma transmission from a cat in a case of toxoplasmosis congenita is reported. It is the first confirmed case of feline toxoplasmosis in Norway. It seems reasonable that pregnant women should be warned against too close contact with sick animals (dogs, cats) even in this country.

Le chat, source de contamination possible dans la toxoplasmose congénitale.

Cas de toxoplasmose transmise par un chat dans un cas de toxoplasmose congénitale. C'est le premier cas authentique de toxoplasmose d'origine féline, décrit en Norvège. Il semble necessaire d'éviter un contact étroit entre les femmes enceintes et les animaux malades (chats et chiens).

Die Katze als mögliche Infektionsquelle bei einem Fall von congenitaler Toxoplasmose.

Es wird über die Toxoplasmaübertragung von einer Katze bei einem Fall von congenitaler Toxoplasmose berichtet. Dies ist der erste gesicherte Fall von Toxoplasmose durch Katzen in Norwegen. Es erscheint berechtigt, schwangere Frauen vor zu engem Kontakt mit kranken Tieren (Hunde, Katzen) zu warnen.

Un caso de toxoplasmosis congénita con posible fuente de infección en el gato.

Se comunica un caso de toxoplasmosis congénita cuya fuente de infección fué probablemente un gato. Es el primer caso de toxoplasmosis felina confirmada en Noruega. Parece razonable aconsejar a las mujeres embarazadas eviter todo contacto con animales enfermos (perros, gatos).

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Morphology of the Pancreas and Glucose Tolerance in Biliary Fistula, in Common Bile Duct Obstruction and after Ligation of Pancreatic Duct

by YNGVE LARSSON

(Summary of Supplement 106)

In non-diabetic rabbits, the absence of bile in the intestine, as is the case in biliary fistula or in ligation of the common bile duct, leads to an increase in the total pancreas parenchyma and in the size of the islet tissue.

In alloxan-diabetic rabbits, the absence of bile in the intestine under the same conditions results in an improvement in the diabetic condition, an increase in size of the islet tissue, signs of regeneration of islet cells, appearance of "Mantelinseln" and a trend to normalization of the alpha cell incidence.

In non-diabetic rabbits, ligation of the pancreatic duct produces, when analyses are made two to three months later, a considerable decrease in size of the islet tissue, although the histologic features indicate the presence of both regressive and progressive changes.

In alloxan-diabetic rabbits ligation of the pancreatic duct results in no change in the diabetic condition, nor in any change in size of the islet tissue in comparison with alloxan-diabetic controls.

Ligation of the pancreatic duct in the rabbit leads to complete resistance to the diabetogenic effect of alloxan, when administered about two months later. The resistance is probbly due to the foetal nature of the islet tissue after this intervention.

Glucose administration subcutaneously for four weeks leads to an average increase in size of the islet tissue in the rabbit, although the individual variation is considerable.

Rabbits submitted to treatment (bile flow obstruction, glucose administration) found to lead to islet hyperplasia are not resistant to the diabetogenic effect of alloxan.

The glucose tolerance (intravenous test) is not significantly increased in rabbits with islet hyperplasia, although a tendency to increased tolerance is

found in biliary fistula animals. Low glucose tolerance is present in under-nutrition, in liver damage, in subtotal reduction of the islet tissue, and in animals with signs of beta cell damage without reduction in size of the islet tissue and without diabetes.

New formation of islet tissue from the duct epithelium in the rabbit is possible even postnatally under certain conditions. Regeneration may also occur by direct stimulation of islet cells. Islet haemorrhage may be a sign of increased islet growth.

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The Histopathologic Changes in the Myenteric Plexus of the Pylorus in Hypertrophic Pyloric Stenosis of Infants (Pylorospasm)

by HILMA ALAROTU

(Summary of Supplement 107)

In this investigation, aimed at determining the histopathologic changes in the myenteric plexus of the pylorus observable in hypertrophic pyloric stenosis of infants, 56 cases have been studied. Eighteen further cases were studied as a control series. Both autopsy and biopsy cases are included in the series. In the autopsy series the sections were taken from the ventral and dorsal walls and from the walls of the lesser and greater curvature. The observations concerned the changes in nerve cells, ganglia and nerve fibers and the occurrence of leukocytes. Altogether more than 2000 ganglia were investigated. The sections, mainly fixed in formalin, were stained for the nerve cell and ganglion investigations with Einarson's gallocyanin–chrome alum stain, using solutions of several different pH values. The nerve fibers were studied from silver stainings according to Bodian's method and the leukocytes from general stainings made with hematoxylin–eosin.

The hypertrophic pyloric stenosis material falls into three series: the biopsy series, the autopsy series without diarrhea, and the autopsy series of cases with diarrhea in addition to hypertrophic pyloric stenosis. In all series similar changes in the nervous system were observed.

The control material falls into two series: the series free of diseases of the digestive system, and the diarrhea series. In the nerve cells and ganglia of the diarrhea series changes were observable in comparison with the control series free of diarrhea. However, these changes were somewhat different from those in the hypertrophic pyloric stenosis series. The pycnotic cells were characteristic of the diarrhea series, as well as the discontinuity of the tissue between the cells. It was found, however, that these changes could not mask the changes in the nerve cells caused by hypertrophic pyloric stenosis.

The principal observations relating to changes in the myenteric plexus

of the pylorus and the conclusions which have been drawn from them may be summarized as follows:

Nerve cells and ganglia of different types and degrees were observed. The nerve cells were divided into four types according to the observed morphologic changes:

Type I: A nerve cell in which the nuclear chromatin is distributed in widely separated masses uniformly over the nucleus, and Nissl substance is distributed in fine granules all over the cytoplasm. Type I has been regarded as a normal nerve cell.

Type II: A nerve cell with a deeply stained nucleolus-nuclear membrane system, which according to Hydén indicates a nerve cell in a state of intense activity.

Type III: A tigrolytic nerve cell, which can be considered in a state of exhaustion according to Hydén.

Type IV: A necrobiotic nerve cell with vacuolization in the cytoplasm and disintegration in the nucleus.

The ganglia were divided into four classes according to the nerve cell types occurring in them:

A ganglion: a ganglion in which the nerve cells of Type I are predominant. This type was considered a normal ganglion.

B ganglion: a ganglion characterized by nerve cells of Type II. In addition to these, nerve cells of Types I and III also occur. The ganglion is thus in a state of hyperfunction.

C ganglion: a ganglion in which nerve cells of Types III and IV are predominant. In addition to these nerve cells of Types I and II may also occur. The number of nerve cells is generally diminished and that of the satellite cells is increased. The ganglion is in a state of exhaustion.

D ganglion: a ganglion containing satellite cells. The nerve cells are absent.

The damage described above was found already to have attained its maximum when the illness, as counted from the onset of projectile vomiting, had lasted 10 days. During the next few weeks there were no noteworthy changes in the lesion, but after about 1 month's duration of the disease a slight recovery begins to be discernible. When the changes are at their maximum, scarcely any A and B ganglia occur at all, the C and D ganglia being dominant. At the commencement of recovery, A and B ganglia appear, and the C ganglia diminish at the same time. The number of D ganglia remains almost constant throughout the period under investigation. The restitution of the ganglia was still incomplete even after 5 months had

elapsed since the onset of the disease, although the clinical symptoms had disappeared. The series still contained B and C ganglia.

The regeneration of the ganglia seems to take place in two separate ways: Cells held in reserve in the ganglion differentiate to constitute nerve cells.

Tigrolytic cells in a state of exhaustion are restored to activity.

From the phase of regeneration satellite cells and cell shadows are left in the regenerated ganglia; moreover the ganglia are frequently of large size.

The nerve fiber bundles are hypertrophied and dilated; further they present a considerable disorder. Thickenings are seen in the individual fibers.

The observations concerning leukocytes in the biopsy series were that in the patients who had been ill for the shortest time these occurred in considerable numbers perivascularly ,and in rather large numbers intraganglionally. With increasing duration of the disease the leukocytes decrease in number and are only rarely encountered when the disease has persisted for more than one month. From the material of the pyloric stenosis autopsy series no conclusions can be drawn with regard to inflammation cells, as other diseases have been simultaneously present.

It seems ovbious that the damage to the nervous system is caused by a pathologic stimulus. This may be a neurotropic inflammation factor of some kind which enters the myenteric plexus of the sphincter. This results in increased nervous activity and in the simultaneous occurrence of phagocytosis by the leukocytes in the inflamed region. To this is added the influence of the increased motility of the sphincteral musculature. These phenomena result in changes in the nerve cells and derangement of the nerves of the opening system which makes the opening muscle unable to perform its function normally.

The clinical symptoms are a consequence of the damage to the nervous system which has been described above. When the stimulation caused by the inflammation subsides, a gradual regeneration of the nerve cells and disappearance of the clinical symptoms sets in. The regeneration takes place at rather a slow rate, since damage is still observable in the nervous tissue 3–5 months after the onset of the disease. Recovery is retarded by the circumstance that after cessation of the inflammation stimulus the pathologic motor simulus still partly persists.

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PROCEEDINGS OF PEDIATRIC SOCIETIES

Pediatric Society of South Sweden

Meeting, October 23, 1955

F. Hedenberg: **Three cases of mutism.**

Three cases of mutism have been taken care of during the last few years in the pediatric department of Falköping Hospital. The first two cases were those of a 10-year-old boy and a 9-year-old girl with elective mutism. The boy was raised in an isolated environment; his father has epilepsy. These factors, in connection with some brain lesion (pathologic EEG), are believed to be the cause of his speech disturbance. Testing shows normal intelligence. The girl's mutism is probably an expression of a serious neurosis, induced very likely by a certain rivalry with a favored younger brother. Testing shows that she has more than normal intelligence. Total mutism exists in a 5-year-old boy. This may possibly be due to a neurotic condition.

None of the patients exhibited any somatic symptoms or auditory defects. They had learned to speak distinctly within the normal time, before they were stricken with mutism. From a therapeutic point of view, these cases have been difficult to manage.

G. Edgren: **Idiopathic tetany.**

Five cases of idiopathic tetany have been treated in the pediatric department of Halmstad Hospital. Two of the cases were sisters. One of the children developed symptoms of Addison's disease in addition and died at 15 years of age. In two cases there was edema of the papillae. (The cases are published in detail in another journal.)

S.-I. Björklund and S. Frieberg: **Polypoid lesions of the colon and rectum.**

In the fall of 1953 a new method for examination of the colon was introduced in the roentgenologic department of the Malmö General Hospital (Andrén *et al.*, *Acta Radiol., 43:* 201, 1955), by which one can diagnose polypi down to 2 mm in size. From September 1953 to October 1955, 119 patients of 1 to 14 years of age and 307 patients from 15 to 29 years were examined according to this method. Polypi were found in 19.2 and 4.5 per cent, respectively. Of the patients with positive findings in the age group of 1 to 14 years, 13 were boys and 10 girls. Eleven of these were 1 to 6 years of age.

The chief symptom of colonic polypi in the age group of 1 to 14 years was rectal bleeding. No patient had anemia, nor any symptom of the type of umbilical colic. The polypi were localized as follows: 5 cranial to the sigmoid, 7 in the sigmoid and 16 in the rectum. By October 1955, 9 of the last-mentioned had been extirpated; all were benign adenomas. Since, according to this investigation, colonic polypi appear to decrease in frequency after 12 to 15 years of age and increase again after 22 years

of age, it seems justifiable to wait, while keeping the patient under roentgenologic control, with the operation of colonic polypi situated beyond the reach of the rectoscope. The low-lying polypi, on the other hand, should be extirpated.

N. Kulneff: **Hereditary agammaglobulinemia.**

In 1952 Ogden Bruton described an 8-year-old boy who had had continual infections for 4 years, e.g. sepsis 19 times, 10 of which were caused by pneumococci. Antibody formation against pneumococci, typhus, diphtheria and parotitis could not be demonstrated or elicited. No gamma-globulin could be demonstrated by electrophoresis. More recently, 20 to 30 similar cases have been reported, all boys. All the described cases of agammaglobulinemia in girls or adults exhibited, in contrast to the boys, anatomic systemic changes, e.g. granulomatosis in the reticulo-endothelial system or sprue. The boys have been assumed to suffer from a congenital, probably sex-linked, hereditary defect of protein synthesis, possibly associated with a deficiency of plasma cells. Familial cases, however, have not been observed previously.

In the pediatric department of Halmstad Hospital, 4 cases with comparable histories have been treated: continual infections, agammaglobulinemia shown by electrophoresis and absence of 7 component on ultracentrifugation. Two are brothers; 2 are cousins with the same maternal grandmother. The ancestors of the patients have lived in the same region, as far as they could be traced (the investigation is not yet completed). The parents are in good health and have normal gamma-globulin.

The patients are being treated with monthly injections of gamma-globulin, at present *c.* 0.1 g per kg body weight. The oldest patient, who did not receive treatment until late in the course, died from bronchiectasis after continuous pulmonary infections; the others are alive with moderate frequency of infection.

The cases are considered to support strongly the earlier assumption that agammaglobulinemia can occur as a sex-linked hereditary disease.

Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, January 13, 1956

J. Ström: **The decrease of breast feeding in Sweden.**

(To be published elsewhere.)

L. Hellström: **About the psychological effects of hospitalization in children.**

As a contribution to the question about the extent of possible psychic changes occurring in children as a consequence of a hospital stay, an investigation of this problem was done at Stockholm's Hospital for Epidemic Diseases. The children investigated all had beta streptococcal infection. This resulted in a homogeneous group in regard to diagnosis and therapy. The epidemic disease laws also forced a stricter isolation toward the environment than is the case in a general children's hospital. The study shows that altogether 28 (17 %) of 159 children exhibited psychic changes, according to the mother. About half of these changes consisted of improve-

ments and half of the children were worse. The study confirms previous investigations in showing that the psychological lability is greater in the younger children. The investigation has not demonstrated any increase of psychological lability from painful complications or measures *per se*.

DISCUSSION.—*A. Wallgren:* The group of children studied is ideal for an investigation about possible psychic effects of hospitalization. If the author will cooperate with a child psychologist and child psychiatrist in planning the continuation of this work, and if he will compare the situation between hospitalized and non-hospitalized patients with scarlet fever, very valuable information should be obtained.

J. Wasserman: How representative are sputum tests?

Secretions obtained by bronchoscopy have been compared with cough plates taken on the same or the following day in order to see how representative sputum tests are from a bacteriological viewpoint. The investigation, which includes primarily tuberculosis and tumor cases and cases for diagnostic workup but only a few real acute bronchial or pulmonary infections, shows that streptococcus viridans and Neisseria—the most common saprophytes in the throat—occur more often in sputum than in bronchial secretions. The situation is similar with beta hemolytic streptococci and most of the gram negative rods. On the other hand, H. influenzae, pneumocci and pyogenic staphylococci which were found in the bronchial secretion were in many cases not seen in the sputum. Thus, examination of bronchial secretions gives surer results than that of the sputum and should be undertaken as soon as bronchoscopy is done for any reason.

DISCUSSION.—*H. Colldahl:* In cooperation with S. Bergman and E. Nilsson I have performed investigations with the aim of studying in how far it is possible to get an idea from examination of the sputum about the presence of a bronchial infection. These studies have shown that bacteria are often forced from the oral cavity to the trachea on bronchoscopy. Because of this, a special method has been worked out which consists of catheterization through a tracheal tube. When examined by this method, at least 90 % of patients without respiratory symptoms had sterile air passages. Asthma patients without elevated sedimentation rate acted like the control group, while those with increased sedimentation rate had bronchial infections more often than the controls.

G. Gille: The early diagnosis of poliomyelitis.

A compilation of the illnesses with which poliomyelitis is generally confused has been made on the basis of the referring physicians' diagnoses. The study is limited to the epidemic of 1953. Three groups can be separated: (1) Illnesses with pareses, e.g. neuritis, polyradiculitis, hysterical paralysis. (2) Illnesses with meningeal signs, e.g. meningitis and meningoencephalitis of various types, menigismus. (3) Illnesses simulating the prodromal signs or general symptoms of poliomyelitis, e.g. all infections accompanied by headache, fever and pain, such as respiratory infections, gastroenteritis, appendicitis, hepatitis etc.

Suspected poliomyelitis	1434	%
Of these poliomyelitis	920	65
No definite diagnosis	42	3
Other diagnosis than polio	472	32

During a polio epidemic the fear of the disease is great. Marked "over-diagnosing" takes place. In comparison with similar studies abroad it is no greater here than in other countries. It is important that no "under-diagnosing" occurs and this has not been the case. Only three patients who had poliomyelitis were sent to the hospital during the period of this investigation with another diagnosis.

Meeting, February 10, 1956

K. *Åkesson:* A case of familiar hypercholesterolemia.

Ten-year-old girl who had three convulsive attacks during the last three months. Partus, birth weight and early development normal. No xanthomata or xanthelasmata. Physical examination not remarkable. Work-up for the convulsions shows a pathologic EEG, but is otherwise normal. BMR normal, cholesterol 410 mg %, total lipids 1160 mg %. Mother has a serum cholesterol of 310 mg % and total lipids of 1125 mg %; father: cholesterol 345 mg %, total lipids 1690 mg %. The parents are not related. Maternal grandfather has cholesterol of 340 mg % and total lipids of 800 mg %. Father's relatives have normal values.

A. *Lundberg:* Epidemic occurrence of myalgia of the calf.

In the spring of 1955, 74 cases of myalgia of the calf of the leg were observed in Stockholm—particularly in school children. They became acutely ill with fever and prodromal symptoms of headache and catarrh. When the prodromal symptoms had disappeared and the fever was in its final stage, i.e. 3–4 days after the onset of illness, leg pains began. These reached their maximum when the patient was free of fever and they disappeared after three days. The myalgia was often so severe that difficulties in walking were noted. The child preferred to walk on the toes with bent knees; it appeared as if stretching hurt more than contraction. There was tenderness on palpation, usually within a limited area in the upper part of the calf. Aside from the gait, the neurological examination was normal.

Sedimentation rate was moderately elevated, there was a definite tendency to leukopenia. The CSF was normal without increase in cells or elevation of protein. One third of the patients examined with EEG had normal tracings; in a few cases changes suspicious of encephalitis were noted, and the rest showed a non-specific dysrhythmia. EMG was performed in three cases, all of which were normal. Muscle biopsy was taken in two cases. The muscle fibers showed non-specific degenerative changes in both. (Ivemark.) Virologic studies are being done. The cases occurred within a limited period of time and the concentration in certain schools, classes and families speaks in favor of a contagious etiology. The incubation period seems to be about 2–10 days. The treatment was purely symptomatic. Prognosis appears to be good. No similar condition has been described in the literature. Since we do not know the etiology of this illness, we have given it a purely descriptive name: Myalgia cruris epidemica. Difficulties of differential diagnosis occur especially with aparalytic polio, encephalitis and polyradiculitis. The particularly biphasic beginning of the illness, the absence of neurologic symptoms and the normal CSF may indicate the correct diagnosis during the early stage of the illness. Are the calves a "locus minoris resistentiae" in these patients of whom the great majority are children? It is known that severe strain plays a part in the involvement of muscle groups in polio, polyradiculitis and myoglobinuria.

C. G. Bergstrand, T. Fahlén, and A. Thildén: **Follow-up examination of meningitis patients.**

Follow-up examination of 92 patients from 0 to 15 years with acute septic meningitis who were treated at Crown Princess Lovisa's Children's Hospital and The Hospital for Epidemic Diseases during the years 1947–1954. Seven of the children died during the meningitis. The mortality was higher in infants and small children. We were able to get information on 78 of the 85 survivors. With a few exceptions, we examined them personally. The number of patients with sequelae was 14. The damages are distributed as follows: Retardation 5, hydrocephalus 2, convulsions 4, pareses 7, ataxic disturbances 3, auditory defect 5, and vestibular disturbance 5. Thus, in most cases there are serious sequelae. Of the 14 patients with sequelae, 9 had received streptomycin and five were treated in some other way. Three of the five patients showing vestibular damage had been treated with streptomycin and 2 had been given other treatment.

G. Christiansson and B. Karlsson: **"Sniffing"—a form of self-intoxication among children. Toxicological viewpoints.**

An examination of 32 boys of school age who, for varying periods of time, exposed themselves to paint thinner through inhalation, has shown reactive bone marrow changes in 10 cases together with basophilic stippling of red blood corpuscles and enlargement of the liver. The observed changes could be due to the high concentration of toluol in the thinner. A toxic effect due to the possible occurrence of extremely small amounts of benzol in the thinner can, of course, not be completely ruled out. The acute effect of sniffing paint thinner consists of an agreeable inebriation with, according to our opinion, great risk of habit formation. The continued careful control of these boys should tell us if the observed changes are reversible and if the cerebral effect leads to demonstrable damage.

S. Ahnsjö: **Pre-school children in summer camp.**

Psychiatric examination of 186 children of the ages 2½ to 8½ years who spent the summer of 1954 in a camp. The material consisted of a highly selected clientele with 29 % from incomplete homes. Only 3.8 % were born out of wedlock while 21.0 % had divorced parents; 55.8 % had two or more siblings and 15.8 % had been in day nurseries previously. The investigation was composed of three separate parts. The first part consisted of observations made by the personnel taking care of the children and was designed to show possible anxiety reactions on departure for the summer colony and then particularly during the first and fifth weeks in the colony. The second part included the author's own examination of the children during the sixth week of their stay. Physical as well as psychological symptoms and signs were noted. The third part of the study was performed by a child psychiatric social worker by means of a home visit after the child's return from the colony. This part of the investigation included a detailed history with special attempts to elicit the child's disposition before the stay at the colony and an analysis of the child's reactions after its return home, together with complementary information about the parents' idea of and attitude toward the colony stay. Significant "nervous" symptoms in the form of anxiety and fear were shown—according to the colony personnel—by about half (48.9 %) of the children. There was a clear-cut dividing line at the age of five years; 76.9 % of the children under five years had such symptoms, while they occurred in only 33.9 %

over this age. Physical symptoms in the form of bed wetting, daytime wetting and encopresis increased noticeably. Bedwetting increased in frequency from 12.4 % before arrival at the colony to 25.3 %, wetting during daytime from 1.1 % to 11.8 %, and the frequency of encopresis from 1.1 % to 12.4 %. This was especially so among the children under five years with frequencies during the colony stay of 41.5, 26.2 and 29.2 %, respectively.

Psychological symptoms pointing to ordinary activity and spontaneity decreased during and after the colony stay while symptoms of passiveness of different types increased markedly during their stay and remained increased thereafter. Of six children who appeared to show clearly damaging effects of the environment during the examination in the sixth week, only two exhibited continued signs of a serious nature after their return home. The age of five years was also a definite dividing line for psychological symptoms so that, from a practical point of view, this age should be considered when indications for and against stay at a summer camp are discussed.

C. Ekström and S. Hagberg: Hepatomegaly of the Budd-Chiary type.

The case concerns a 10-year-old boy who became ill at the end of February 1955 with pain and cramps in the epigastrium occurring after meals. At the end of January he had received trauma to the abdomen which had not been considered significant at the time and which was not reported in the original history. Examination revealed a liver enlarged to the level of the umbilicus and ascites. Liver biopsy showed central lobular stasis with distension of the central veins and occasional hemorrhages. The liver cells in the central part of the lobules showed necrosis. Splenography was performed and the earlier impression was verified that there must be obstruction of the outflow of blood from the liver—so-called Budd-Chiari syndrome. At the operation on 11 July 1955 bluish discoloration of the liver was found high on the right convexity. An incision was made there through which a finger could be introduced. A hole could be felt centrally in the liver and blood spurted from this under high pressure. The localization of the hole was such that one could imagine quite well that it might press on the hepatic veins when distended. The cavity was drained with a large tube. The condition of the patient improved. The variations in the size of the liver was followed by means of roentgenograms. Four months after operation the liver had decreased by 30 %. At the same time a new biopsy was taken and this showed a marked regression of the central lobular damage. The authors interpreted this as a case of intrahepatic liver rupture with a history of trauma in which the diagnosis could be made due to extensive exposure on exploration. The cause of the syndrome was attacked and in this way the patient could be helped and should have a good prognosis.

BOOK REVIEWS

Advances in Pediatrics. Edited by *S. Z. Levine*. Vol. 7.

The Year Book Publishers. Chicago, Ill., 1955. Price 8 dollars.

The seventh volume of this excellent series of books contains the following 7 monographs: J. Caffey: On Fibrous Defects in Cortical Walls of Growing Tubular Bones; M. F. Campbell: The Urinary Tract in Childhood; F. Gomez *et al.*: Malnutrition in Infancy and Childhood, with Special Reference to Kwashiorkor; E. Mannheimer: Phonocardiography in Children; M. A. Perlstein: Infantile Cerebral Palsy; H. Schwachmann *et al.*: Mucoviscidosis; O. Swensson: Congenital Megacolon. The volume should be kept as a valuable reference book in every pediatric library.

Pediatric Clinics of North America. Symposia on Unusual Infections of Childhood; Laboratory Tests and Special Procedures. Febr. 1955.

W. B. Saunders Company, Philadelphia.

The first half of this volume deals with a variety of infectious diseases, which the average pediatrician rarely encounters. It will serve as a ready reference book and guide for the diagnosis and care of unusual infectious diseases in children. Factual knowledge is reported on Tularemia, Smallpox and Vaccinia, Cat Scratch Disease, Aseptic Meningitis Syndrome, Leptospirosis, Moniliasis and Toxoplasmosis. The second half of the book gives a description of laboratory tests and methods in examination of liver, kidney, pancreas, endocrine organs, and bone marrow. In addition there are special chapters on blood pressure and blood protein measurements, on bronchography, EEG and on the value and clinical application of determining bacterial sensitivity to antibiotics. The last chapter deals with fluid and electrolyte therapy. Like the previous volumes this one is written by specialists in different fields of pediatrics and keeps the high standard of its predecessors.

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From the Royal Hospital for Sick Children, Glasgow

The Effect of the Ingestion of Potassium Salts on the Excretion of Sodium-Retaining Corticoids in the Human Subject

by H. ELLIS C. WILSON

It has been shown in the normal human subject that the plasma potassium concentration falls slightly after the ingestion of acid potassium phosphate and of the potentially alkaline citrate salt of potassium. The usual potassium diuresis nevertheless follows. These results would appear to show that any direct effect of the plasma potassium on the rate of excretion by the kidney is unlikely. Similar investigations on children in the post-absorptive state showed in general that the rate of potassium excretion tended to vary inversely to the plasma level of potassium. The conclusion was drawn that the rate of excretion of potassium was controlled in some way by the state of the tissues with respect to this electrolyte (Wilson). The present investigation was carried out on the assumption that this process might be effected by some hormone. The recent discovery of aldosterone and its effect on the Na/K ratio in the urine of adrenalectomised rats suggested that it might be responsible (Tait *et al.*). Recent investigations in the normal human subject, while on a salt poor diet, have shown small increases in the excretion of a sodium-retaining corticoid (Alexrad *et al.*), but hitherto little work has been done in humans on the possible influence of potassium salts on the excretion of this corticoid (Gaunt *et al.*). The experiments reported here were carried out to test this hypothesis.

Methods

The investigations were repeated on the same subject as in the previous report. A dose of approximately 1 g of potassium (3 g KH_2PO_4 or 3 g K citrate) dissolved in 125 ml of distilled water was ingested in each experiment: urine was collected in the following periods.

1. Pre-period before potassium ingestion (3 hours).
2. A diuresis period 1st to 3rd hour after K (3 hours).
3. A post-period 3rd to 6th hour after K (3 hours).

This procedure was carried out at the same time each day with an interval of at least one day in between; all urines were immediately put in the ice chest. The urines

from the corresponding periods were pooled until sufficient had been collected for extraction and assay. They were then extracted without acidification exactly according to the method employed by Cope and Garcia-Llaurada. The extract was dissolved in 20 % ethyl alcohol so that the dose for assay was contained in 0.1 ml. Three separate sets of assay were carried out: the first on male rats 120–150 g weight. These received a loading dose of 5 ml 0.9 % NaCl intraperitoneally and 0.1 ml of extract equivalent to 3 hours urine. The controls received the saline and 0.1 ml 20 % alcohol. The second assays were carried out on male rats of 60–80 g weight: these received a loading dose of 2 ml 0.9 % NaCl and 0.1 ml extract equal to 1½ hours urine. The third assay was also carried out on urine collected during the same hours of the day except that no potassium salts were taken. This was in order to exclude a possible normal diurnal variation in the output of the corticoid. Sodium and potassium were estimated by the flame photometer.

Experimental Results

The effects of ingestion of potassium salts on the plasma level were repeated (Fig. 1). It will be seen that the usual fall was seen with the acid or alkaline salt except on one occasion, when the salt had been taken for three consecutive days. This point will be discussed later. The usual diuresis followed over a period of 6 hours (Table 1).

TABLE 1

Excretion of Na and K after 1 g of K as KH_2PO_4.

	Na mg per hour	K mg per hour	Na/K ratio
Pre-period			
3 hours	47.3	72.0	0.68
K diuresis period			
3 hours	73.5	193.5	0.44
Post-period			
3 hours	93.0	101.2	0.91

Assays

The assays in Table 2 Group 1 show that there is an increase in the amount of a sodium-retaining corticoid as judged by the fall in the Na/K ratio from the pre-period to the post-period. The crucial test, whether the difference in the ratios between the pre-period and one or both of the following periods is statistically significant, appears to be satisfied for the post (3rd to 6th hour) period. The assays in Group 2 were intended to confirm the results with smaller rats and a smaller dose and to concentrate on the post-period. These results show that the differences between the pre-period and

TABLE 2

	Na/K ratio
Group 1	
Control period	1.44
Pre-period	1.47
K diuresis period	1.34
Post-period	0.96

Differences of ratios pre-period : post-period 0.51.
4 experiments. 18 rats in each group.
$t = 2.6$ $(0.05 > P > 0.02)$.

	Mg per 100 g rat per 3 hours		Na/K ratio
	Na	K	
Group 2			
Control period			
3 Exps. 13 rats in each group	3.55	2.56	1.39
Pre-period			
9 Exps. 30 rats in each group	2.70	3.0	0.96
Post-period			
9 Exps. 30 rats in each group	2.5	3.9	0.66

Difference of ratios pre-period : post-period = 0.3.
$t = 1.9$ $(0.1 > P > 0.05)$.
Groups I & II. Difference of ratios pre-period : post-period = 0.36.
$t = 3.2$ $(0.01 > P > 0.001)$.

	Na/K ratio
Group 3	
Pre-period (6 rats)	0.69
Post-period (6 rats)	0.90

the post-period are almost significant. If the two groups of figures are taken together, however, $P < 0.01$. The object of the third asssay was to eliminate the possibility of a normal variation in the amount of sodium-retaining corticoid excreted during the same hours of the days when the potassium diuresis experiments were being carried out. The ratios are not significantly different, indeed the post-period has altered in the opposite direction.

Discussion

These results would appear to show that the ingestion of potassium salts by mouth causes an increase in the amount of a sodium-retaining corticoid

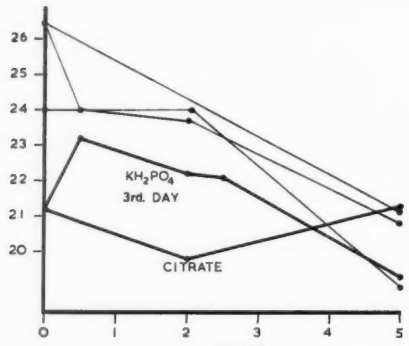

Fig. 1.

in the urine and probably in the blood. The problem however is, by what mechanism is an increase of the hormone in the blood effected. As the plasma potassium does not rise after taking it by mouth, any direct effect of this ion on the pituitary or adrenal gland would appear to be excluded. The following scheme is hence put forward. It is suggested that the extra potassium coming to the liver where it can be temporarily retained, inhibits the breakdown by this organ of a sodium-retaining corticoid such as aldosterone. The increase in the corticoid in the blood would then stimulate the kidney to excrete more potassium relatively to sodium, the plasma potassium would tend to fall as observed, until topped up by release from the liver. This process would continue until most of the potassium had been excreted. If the capacity of the liver to retain potassium were exceeded, as on the third day (Fig. 1) it is conceivable that some should be released in advance of its excretion by the kidney and hence the slight increase in level noted on this occasion. This hypothesis gives the liver a controlling and not a secondary role in maintaining a certain level of corticoid in the blood and hence in the excretion of potassium. Hence the liver appears to play the same part in relation to salt corticoid level in the blood as the pituitary does in relation to the other corticoids, although there appears to be no necessity as yet of postulating a substance analogous to ACTH. This conception is in keeping with the fact that not all the adrenal gland degenerates after removal of the hypophysis. The residual active part is supposed to secrete the salt corticoids. Further it has been shown that ACTH has little or no effect on the output of aldosterone and that the factors controlling its secretion are obscure (Gaunt *et al.*). The liver moreover is known to be an organ concerned in the breakdown and disposal of corticoids but so far not in a controlling role in relation to body requirements (Bongiovanni & Eisenmenger). These observations may have pathological significance. If

he liver responds to exogenous potassium by release of a corticoid into he blood it would appear reasonable to assume that it should do the same f supplied from an endogenous source. There are several conditions fre- uently characterised by oedema; salt retention, an increase in sodium- etaining corticoid in the urine (Singer, Luetscher), and a loss of potassium rom the body cells, such as occurs in nephrosis (Fox & Slobody), and ongestive heart failure. It is suggested that the release of potassium from he tissues in those conditions may be partially responsible for stimulating he liver to release a salt corticoid and thus cause sodium retention. It is lso suggested that the post-traumatic sodium retention may be caused y the loss of potassium usually found in this condition. Such a post- raumatic increase in the sodium-retaining corticoid has been noted (Garcia- Llaurada). It should be kept in mind that the results have been obtained n chloroform extracts of urine which contain substances other than aldo- sterone which may condition its activity. In this connection the figures in Table 2 Group 2 assay may be of significance. The total electrolyte excretion has been calculated for all experiments per 100 g rat for 3 hours. It will be noted that the decrease in the Na/K ratio from the control to the pre-period is effected largely by a decrease in sodium excretion. On the other hand, the fall in the ratio from the pre-period to the post-period has been effected largely by an increase in the potassium output.

I am indebted to Professor R. C. Garry for his helpful criticism.

Summary

The ingestion of potassium salts by the normal human subject is associated during the ensuing diuresis, with an increase in sodium-retaining corticoid in the urine while the plasma potassium level falls.

The liver appears to play a controlling and no mere passive role in maintaining the level of a salt corticoid in the blood and hence indirectly in the metabolism of sodium and potassium.

This effect of potassium salts on the liver may play a part in pathological conditions such as nephrosis and congestive heart disease, where there is a loss of potassium from the tissues and an increase of a sodium-retaining corticoid in the urine.

L'effet de l'ingestion de sels de potassium sur l'excrétion des corticoïdes retenants du sodium dans l'homme.

L'ingestion de sels de potassium par l'homme normal est, pendant la diurèse consécutive, associée à une augmentation du corticoïde retenant du sodium dans l'urine. En même temps le taux de potassium plasmatique est diminué. Le foie semble contrôler activement le taux du corticoïde de sel dans le sang. Il contrôle donc aussi, indirectement, le métabolisme de sodium et de potassium. L'effet des sels de potassium sur le foie peut être important dans des conditions pathologiques comme la néphrose et les défaillances cardiaques congestives, où les tissus perdent du potassium et où le corticoïde retenant du sodium est augmentés dans l'urine.

Die Wirkung von Kaliumsalzen auf die Ausscheidung von natriumretinierenden Corticoiden beim Menschen.

Die Aufnahme von Kaliumsalzen ist beim normalen Menschen während der nachfolgenden Diurese von einem Anstieg der natriumretinierenden Corticoide im Urin begleitet, während der Kaliumspiegel im Serum sinkt. Die Leber scheint eine überwachende und nicht nur passive Rolle zu spielen, indem sie den Salzcorticoidspiegel im Blut aufrechterhält und daher indirekt den Natrium- und Kaliumstoffwechsel. Diese Wirkung von Kaliumsalzen auf die Leber mag bei pathologischen Zuständen, wie Nephrose und congestiven Herzerkrankungen, eine Rolle spielen, wo ein Verlust von Kaliumsalzen aus dem Gewebe und ein Anstieg der natriumretinierenden Corticoide im Urin besteht.

Efecto de la ingestión de sales de potasio sobre la excresión de corticoides retensores de sodio en el hombre.

La ingestión de sales de potasio por el hombre normal se asocia, durante la diuresis posterior, con un aumento del corticoide que retione sodio en la orina mientras el nivel plasmático de potasio decae. El hígado parece ejercer un control y un rol no meramente pasivo en el mantenimiento del nivel de mineralocorticoides en la sangre y por lo tanto indirectamente en el metabolismo del sodio y potasio. Este efecto de las sales de potasio sobre el hígado puede desempeñar un rol en condiciones patológicas como la nefrosis e insuficiencia cardiaca congestiva, donde existe una pérdida de potasio a nivel de los tejidos y un aumento del corticoide que retiene sodio en la orina.

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Acute Osteomyelitis in Infancy

by B. WOLMAN

Acute osteomyelitis may occur at any age from the newborn period onwards, and usually develops as a result of a septicaemia or from local trauma or sepsis.

The disease is now usually regarded as being uncommon. Certainly the incidence and severity have decreased in the past fifteen years, firstly because we have a better knowledge of the treatment of the sick child and secondly because of the advent of the antibiotics. However, in the past three years, nine infants under the age of six months and nine older children with this disease have come under my care.

This first group of nine infants is thought to be of sufficient interest to warrant reporting (Table 1). In all but three cases the disease started in the neonatal period, that is within the first month of life, the youngest being nine days old.

In all but one of the infants (Case 7), the disease was preceded by a minor infection such as a mildly septic umbilicus, paronychia, conjunctivitis or a purulent nasal catarrh. In each case the infection appeared to be a mild one for which no special treatment had been considered necessary, or alternatively had been confined to very simple measures.

This sepsis had persisted for varying periods up to seven days and then had been followed by the usual clinical picture of osteomyelitis. The outstanding local symptom was swelling at the affected site and in the case of involvement of a long bone, loss of function of a limb.

In seven babies, there was swelling of the involved parts—the right thigh in three cases, the left thigh in two cases and the left arm in two cases, and loss of use of the limb so that the mothers of the three oldest babies were worried about the possibility of poliomyelitis. In fact in two of these cases because of the slightness of the preceding sepsis, the diagnosis of scurvy was considered.

In two of the youngest babies there was a purulent nasal discharge followed by, or associated with, swelling and induration of the right side

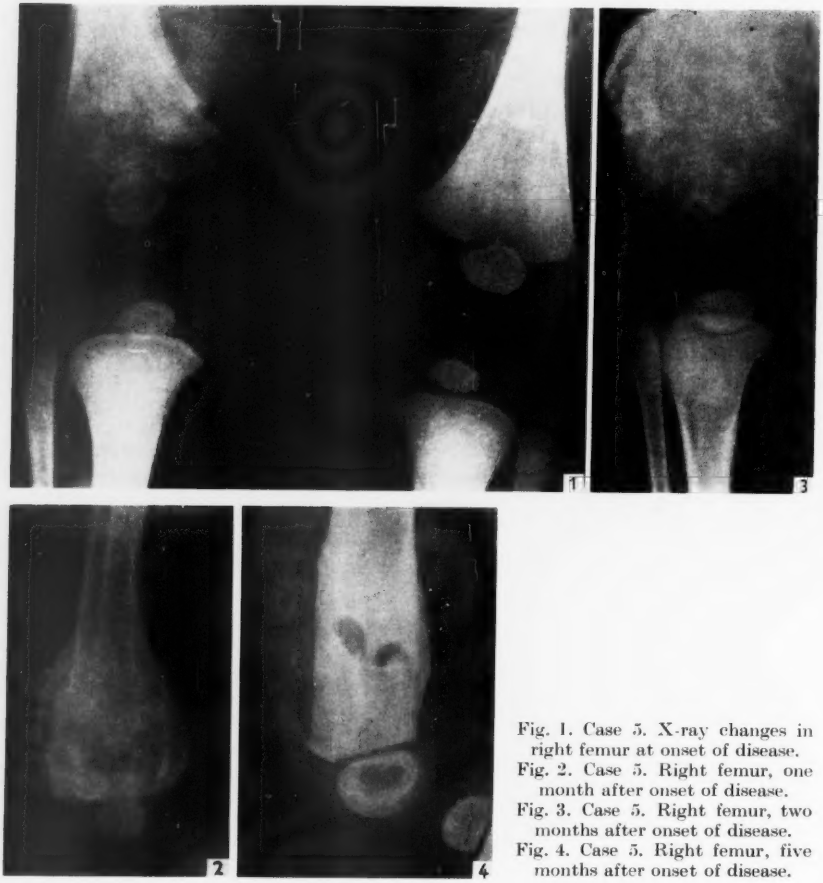

Fig. 1. Case 5. X-ray changes in right femur at onset of disease.
Fig. 2. Case 5. Right femur, one month after onset of disease.
Fig. 3. Case 5. Right femur, two months after onset of disease.
Fig. 4. Case 5. Right femur, five months after onset of disease.

of the face extending from below the eye to the side of the nose and down to the upper lip. Here the infection possibly started in the maxillary antrum or in a developing dental sac.

The striking feature about the disease was the general good condition of the infant. In each case the temperature was hardly more than 100 and the baby had been feeding well without vomiting. Apart from irritability and crying when the affected part was handled, there was no generalised systemic upset. Because of the minimal original infection and the good general progress of the infant, the diagnosis is often made late, and as the disease is thought to be uncommon especially in this age group, even not considered.

The infecting organism was obtained on blood culture in six of the nine cases, and in each of these cases was a Staphylococcus aureus coagulase positive. The same organism was obtained from the culture of the pus from the original site of infection in five cases out of the six, suggesting a septicaemia had followed the original infection. In two of the other three cases the same organism was obtained, in pus from the joint (Case 8) and in the umbilical discharge (Case 9). Except in two cases (Cases 5 and 9), the staphylococcus was found to be penicillin resistant but sensitive to the other antibiotics. The predominance of the staphylococcus was interesting and confirms the tendency of the paediatrician to blame this organism more than any other for neonatal sepsis. It has superseded in importance and virulence the haemolytic streptococcus in this age group and therefore these findings are in agreement with those of Blanche in Los Angeles in 1952 and differ from those of Green reported from Boston in 1935.

X-rays were taken of the affected parts in all cases, but it was unusual to find any abnormality at the onset of the disease and in fact no radiological abnormality was detected at all in four cases. The absence of radiological abnormalities, however, does not invalidate the diagnosis. Periosteal elevation and calcification developed after seven to ten days in two cases and became extensive. Several X-ray pictures show the changes which take place and, as healing progressed, the gradual re-absorption of this new bone, and return to normal.

Treatment was carried out by intensive systemic therapy using the appropriate antibiotics until all signs of inflammation had disappeared. Because of the penicillin resistance, streptomycin (250 mg twice daily intramuscularly) was the drug of choice, and a wide range antibiotic such as terramycin (50 mg per lb = 100 mg per kg body weight per day) was given in addition. The local signs, raised temperature and white cell count, if elevated, usually subsided within three or four days but treatment was continued until the blood sedimentation rate had returned to normal, which varied from a three to six or eight weeks. Treatment included oral vitamin B and careful observation in case of the development of thrush in the mouth. No deafness was noted at follow-up in any child.

Results

A good eventual result was obtained in all cases, with no residual disability.

In one baby with osteomyelitis of the maxilla, there was a mild degree of relapse occurring one month after cessation of six weeks' treatment. Minimal swelling re-occurred with a local purulent point at the inner end of the maxilla but this settled down without any surgical interference after two further weeks of treatment.

In the other case of osteomyelitis of the maxilla, two upper incisor teeth extruded and were eventually removed.

In two other cases there was a relapse after the initial treatment had been completed. A small localised abscess at the inner aspect of the thigh developed and began to discharge thin pus and continued to discharge until a minute piece of sequestrum, no bigger than a grain of rice, was extruded. The discharge then ceased, the wound healed and the child has had no further trouble. The follow-up has been eighteen months and $2\frac{1}{2}$ years respectively.

In only two of these cases was there a septic arthritis in association with the bone lesion. In addition to general systemic treatment these infants had daily aspiration of the joint carried out until no further pus was obtained. Immobilisation was maintained by a plaster shell and intensive physiotherapy was given to the quadriceps muscle for twelve months and six months respectively. There is no residual disability at the present time and both children walk perfectly well.

This paper was read at the Annual Meeting of the Manchester Paediatric Club in September, 1955, and I am grateful to several colleagues for their helpful criticism and advice.

Mrs. Laycock of the Department of Clinical Photography, Birch Hill Hospital, was responsible for the photographs.

Summary

Nine cases of acute osteomyelitis in infancy are described. In all but one of the infants the disease was preceded by a minor infection without any marked systemic disturbance. In each case the infant seemed to be in good general condition in spite of the disease which was shown by local swelling and/or loss of function.

Staphylococcus aureus (coagulase positive) was the organism obtained on blood culture in six of the nine cases and this organism was also grown from pus obtained at the site of the original infection in two of the other three cases.

Prolonged treatment with appropriate antibiotics was invariably successful.

It is concluded that acute osteomyelitis is still a common disease in infancy which should be treated as an urgent medical emergency. Surgical treatment is now hardly ever needed.

L'ostéomyélite du nourrisson.

Neuf cas d'ostéomyélite aigüe de nourrissons sont décrits. Dans tous les cas, excepté un, la maladie était précédée par une infection insignificante sans disturbation systémique marquée. Tous les nourrissons étaient en bonne condition générale malgré la maladie qui se manifestait par un gonflement local et/ou une perte de fonction. Dans 6 de ces 9 cas l'hémoculture démontrait des staphylocoques doré (positifs à la coagulase). Le même organisme était cultivé du pus obtenu à la place de l'infection primaire dans deux des trois cas restants. Un traitement prolongé avec des antibiotiques appropriés

était toujours couronné de succès. En conclusion, l'ostéomyélite aigüe est encore une affection commune dans l'âge de nourrisson qui doit être traitée comme un cas d'urgence médicale. Aujourd'hui un traitement chirurgical n'est guère nécessaire.

Akute Osteomyelitis im Säuglingsalter.

Neun Fälle von akuter Osteomyelitis im Säuglingsalter werden beschrieben. In allen Fällen ausser einem ging der Erkrankung eine leichtere Infektion ohne irgendwelche ausgesprochenen Allgemeinstörungen voraus. Regelmässig schienen die Säuglinge trotz der Erkrankung, die mit lokaler Schwellung und/oder Funktionsverlust einherging, in gutem Allgemeinzustand zu sein. Staphylokokkus aureus (Koagulase positiv) konnte in 6 von 9 Fällen im Blutkulturen gezüchtet werden und dieser Keim wurde auch in dem Eiter nachgewiesen, der bei zwei von den anderen drei Fällen am Ort der Primärinfektion gewonnen werden konnte. Langdauernde Behandlung mit entsprechenden Antibiotica war regelmässig erfolgreich. Es wird abschliessend gefolgert, dass die akute Osteomyelitis immer noch eine geläufige Erkrankung des Säuglingsalters ist, die als dringendes medizinisches Ereignis behandelt werden sollte. Chirurgische Therapie wird jetzt kaum mehr benötigt.

Osteomielitis aguda en el lactante.

Se presentan 9 casos de osteomielitis en lactantes. En todos menos uno, la afección fué precedida por pequeñas infecciones sin marcado disturbio general. En todos los casos el lactante presentó buen estado general a pesar de la enfermedad la cual estuvo representada por inflamación local y/o pérdida de la función. En seis casos el hemocultivo mostró estafilococo dorado (coagulasa positiva), organismo que también fué encontrado en el pus de 2 de los 3 casos restantes. El tratamiento prolongado con antibióticos fué invariablemente seguido de éxito. Se concluye que la osteomielitis aguda sigue siendo una enfermedad común en los lactantes y debe ser tratada como una urgencia médica. El tratamiento quirúrgico es raras veces necesario.

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From the Children's Hospital, University of Oslo, Norway
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Erythrocyte Production and Iron Stores in Premature Infants During the First Months of Life

The Anemia of Prematurity–Etiology, Pathogenesis, Iron Requirement

by MARTIN SEIP and SVERRE HALVORSEN

The main purpose of the investigations to be reported has been to study the erythrocyte formation and iron stores in premature infants, in order to elucidate the etiologic and pathogenetic factors in the early anemia of prematurity and the iron requirements of premature infants.

Premature infants with birth weights below 2000 g who were treated in the Children's Hospital, University of Oslo, have been studied. The main series includes 16 infants, 8 of whom weighed less than 1500 g at birth. An additional 13 prematures and a number of full-term infants have been studied in less detail.

The premature infants were treated in incubators at a temperature of 32–33° C until they reached a weight of 2000 g. Oxygen was administered only on strict indications, and then in moderate concentrations. One infant with prolonged asphyxia received oxygen for six weeks after birth, the others received either no extra oxygen, or only for a few days. The diet consisted of human milk for about 8 weeks, subsequently of cow's milk. From the fourth day of life, supplements of A, C, D vitamins and skimmed dried milk were given. Iron medication was not given until the bone marrow was found to be hemosiderin-free. One infant died of bronchopneumonia at the age of 5½ weeks. Five of the sixteen had short cyanotic spells. No other serious complications were recorded.

Methods

Erythrocyte production was evaluated by means of meticulous reticulocyte counts, using a method described by Seip. Reticulocyte counts were performed twice a week by one observer (M. S.). Because all red blood cells normally leave the blood-forming organs as reticulocytes, reticulocyte counts, when performed by an accurate method, give reliable information concerning changes in rate of erythrocyte production.

Iron stores were studied in bone marrow preparations stained by the Turnbull stain, which in the authors' opinion gives better preparations than Prussian blue, originally used by Finch. Tibial punctures were performed, and about 1 cc of bone

marrow was aspirated. The aspirated fluid was mixed in a Petri dish with 1 cc sodium citrate solution (3.1 per cent). Visible fragments of bone marrow tissue were collected, fixed in 10 per cent formalin-alcohol, embedded in paraffin, sliced and stained. The slides were evaluated and graded according to Finch from 0 to 6 by one observer (S. H.).

Sometimes, particularly in newborns, it was difficult to obtain enough marrow tissue. Therefore, bone marrow biopsies were also taken immediately after death in four prematures who died shortly after birth from diseases that probably could not have influenced the babies' iron stores.

In all, 118 bone marrow punctures were performed. Satisfactory preparations were obtained in 90 of these. The first punctures were done on the third to the fifth days of life. As a rule, the tibial punctures were repeated every four weeks, in some infants every two weeks. In 5 cases one puncture only was performed.

Hemoglobin determinations were done from heel blood with a Sicca hemometer at weekly intervals during the stay in hospital. The hemoglobin percentage was recorded, using Haldane's standard. Red blood cells were counted in a Buerker counting chamber. Intensity of growth was followed by means of daily weighings.

Results

It will be seen from Fig. 1 that the hemoglobin values followed the well-known trend, with a marked drop during the first eight weeks of life. A similar, though less pronounced decrease is found also in full-term infants. The premature infants with the lowest birth weights on an average show the lowest hemoglobin levels in this period of life, with a minimum of about 60 per cent, in comparison to 70 per cent for those weighing more than 1500 g at birth.

The reticulocyte levels, and hence the rate of erythrocyte formation, appear from Fig. 2. For a few days after birth, rate of red blood cell formation is high, then rapidly decreases to a low level at 1–2 weeks of age. A period of relatively low erythropoietic activity follows. This period is short (1–2 weeks) in the smallest infants (birth weights below 1500 g), somewhat longer (3–4 weeks) in the heavier prematures, and longest in full-term infants. It is replaced by a period of intensive, and, in the smallest prematures, even highly intensive erythrocyte regeneration with high reticulocyte values.

Using the described method, the average number of reticulocytes was found to be 1.57 per cent in healthy adults. Reticulocyte values above 2 per cent indicate an increased rate of erythrocyte formation. Fig. 3 illustrates the infants' age in weeks, when the first signs of increased red cell regeneration (i.e. reticulocyte values higher than 2 per cent) could be demonstrated, in relation to the birth weights. We see that signs of increased blood regeneration occur at an earlier moment in infants with the lowest birth weights, than in those with higher birth weights.

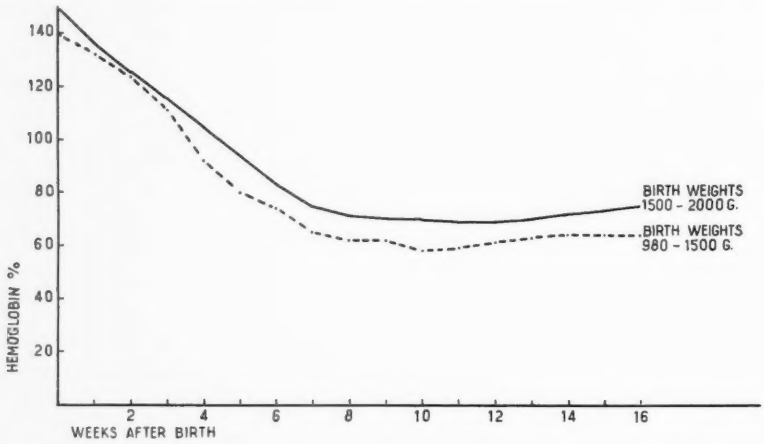

Fig. 1. Average hemoglobin levels in the present series of premature infants.

Reticulocyte curves for the first months of life similar to ours have also been found by others (Magnusson, Schulman *et al.*, and others). However, previous authors have not paid particular attention to the difference in the various weight groups.

Fig. 4 illustrates the intensity of growth. The weekly weight gain has been expressed in per cent of the infant's weight at the beginning of the week. The black columns show the average weekly weight gain for the 8 prematures in the main series with birth weights below 1500 g, the white columns corresponding figures for the 8 babies with birth weights of 1500–2000 g. The smallest infants showed, relatively speaking, a considerably higher intensity of growth, particularly in the period from the third to the twelfth weeks after birth. From the third to the seventh weeks of life the average weekly weight gain even exceeded 10 per cent in the lowest weight group. The infants weighing 1500–2000 g at birth also showed the highest intensity of growth in the same period.

Comments

The data presented can elucidate several important problems pertaining to the etiology and pathogenesis of the anemia of prematurity, and may also to some extent explain the normal decrease in hemoglobin in fullterm infants in the first months of life.

In several of the most important publications from recent years dealing with the anemia of prematurity (Gairdner *et al.*, Schulman *et al.*), the

transient decrease in erythropoietic activity is maintained to be the most important pathogenetic factor, and next to this growth. These authors think that increased hemolysis is only of minor, if any, importance.

Our data, however, demonstrate convincingly that reduced erythropoietic activity contributes only very little to the postnatal drop in hemoglobin and erythrocyte levels in the smallest premature infants. In the greater part of the period, when these infants show falling hemoglobin values, erythropoietic activity is increased, or even highly increased. The period of reduced erythropoiesis in this group is 1–2 weeks, sometimes shorter, and even in this period erythrocyte formation is evident (Fig. 2). In the heavier prematures, reduced erythrocyte formation plays a somewhat greater role in the pathogenesis of the falling hemoglobin level, although other factors are certainly more important. In full-term infants the period of reduced erythropoiesis is longer, and therefore more important, but does not play the dominating role attributed to it by Gairdner & coworkers.

In premature infants the intensive growth is a much more important and probably the most important pathogenetic factor. However, the drop in hemoglobin and erythrocytes is so rapid, despite a high rate of erythrocyte formation, that it can not be explained by growth alone, but only by the assumption that hemolysis is also considerably increased. We have other strong reasons, too, to suppose that the longevity of fetal red cells is reduced. Hollingsworth in his studied of fetal erythrocytes labeled by radio-chromium found their life span to be considerably shorter than the life span of adult red cells. Künzer's determinations of the amount of bile pigment in the stools, which is relatively high for about 10 weeks after birth, are also strongly indicative of an increased erythrocyte destruction. Probably, the average red cell survival in premature infants during the first weeks of life is less than half the normal survival of adult red cells.

In Fig. 1 the hemoglobin percentage is already falling in the first and second weeks. This apparent decrease is mainly due to the fact that the determinations have been performed with heel blood, which in the first two weeks of life gives unduly high hemoglobin levels and no correct measure of the hemoglobin concentration in the circulation as a whole (Oettinger & Mills). The decrease recorded in the first and second weeks is to the greatest extent due to an adjustment of the hemoglobin level between the different parts of the circulation. The subsequent fall, however, represents a marked, real decrease in the hemoglobin concentration.

In healthy full-term infants erythrocyte production is intensive and remains approximately unaltered for about three days after birth, and then in the next 2–3 days decreases to a low level (Seip). The decrease in reticulocyte values and rate of red cell formation is somewhat delayed in

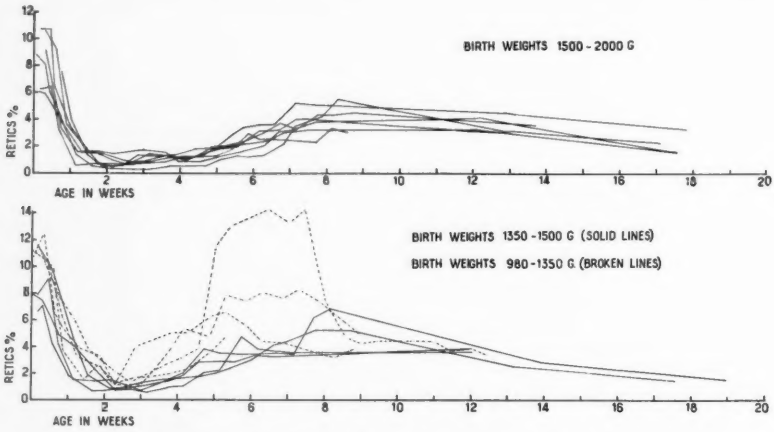
BIRTH WEIGHTS 1500 - 2000 G
RETICS %
AGE IN WEEKS
BIRTH WEIGHTS 1350 - 1500 G (SOLID LINES)
BIRTH WEIGHTS 980 - 1350 G (BROKEN LINES)
RETICS %
AGE IN WEEKS

Fig. 2. Reticulocyte levels in premature infants.

premature infants. But the main features of the reticulocyte curves are alike in premature and full-term infants, and the reasons for the rapid decrease in reticulocyte level and erythropoietic acitivity are the same: (1) the improved oxygen supply, and (2) the transient cessation of growth after birth.

When red cell regeneration after a short or somewhat more prolonged delay again increases, there are also two main causes: diminishing hemoglobin level in the circulating blood, and the resumption of growth. The rate of erythrocyte formation in premature infants in the first months of life is chiefly governed by their hemoglobin level and their intensity of growth.

Other circumstances being equal, the stimulation exerted on the bone marrow by the blood-regulating mechanisms to produce hemoglobin and red cells is the greater, the lower the hemoglobin level. This fact holds true also in infancy (Gairdner *et al.*). From our data we may conclude that the intensive growth in premature infants in this age group is also exerting a marked stimulating influence on erythropoiesis. This relationship between intensity of growth and rate of red cell formation is of course particularly evident in the lowest weight group. A comparison of the black columns in Fig. 4 and the corresponding reticulocyte curves (Fig. 2) demonstrates the close relationship between intensity of growth and reticulocyte levels in this period of life. The reticulocyte curves are lagging slightly behind, because a certain time is required before the full erythropoietic effect of an increased rate of growth can be achieved.

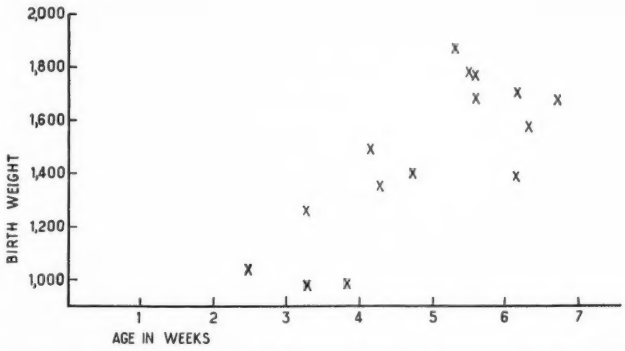

Fig. 3. The age in weeks, when signs of increased red cell regeneration (reticulocyte values higher than 2 %) could be demonstrated in relation to the birth weight.

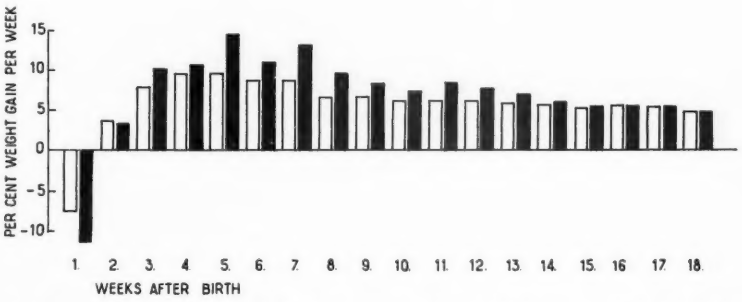

Fig. 4. Average weekly weight gain in the present series. White columns: Infants with birth weights 1500–2000 g. Black columns: Infants with birth weights 980–1500 g.

The effect of growth on erythropoiesis is brought about in two ways. Growth leads to an increase in blood volume with a following dilution of the blood, and falling hemoglobin levels, which in turn leads to a stimulation of the bone marrow. However, it emerges from a detailed study of our data, especially for the smallest prematures, that growth may stimulate erythropoiesis *before* a greater decrease in hemoglobin takes place. In our opinion this must be because growth requires an increased oxygen consumption and, thereby, an increased demand for oxygen-carrying cells occurs.

Gairdner *et al.* have pointed out that in full-term infants erythropoietic activity is low, until the hemoglobin concentration has dropped to 11–12 g/100 cc of blood (75–80 per cent), and that the bone marrow is not stimulated to an increased red cell production until this level is reached. He considers this hemoglobin level to be "normal" in infancy. This is not

entirely so in premature infants in the period of most intensive growth. In these signs of increased erythrocyte formation (reticulocyte values above 2 per cent) can often be found several weeks before such a low hemoglobin level is reached. In our series the infants with the most rapid growth spurts presented signs of increased erythropoietic activity while the hemoglobin content of the blood was still more than 100 per cent. In 9 out of 16, reticulocyte values higher than 2 per cent, and often considerably higher, were found while the hemoglobin concentration was still 90 per cent or above. Of these, 6 were in the group with birth weights 980–1500 g.

The lowest hemoglobin levels are found from eight weeks of age. However, in many cases the highest reticulocyte counts (i.e. the most active erythropoiesis) were found before eight weeks of age. The subsequent decrease in erythropoietic activity is thought to be due to the decreasing rate of growth from the seventh or eighth week.

These facts make it clear that the blood-forming organs are stimulated at a higher hemoglobin level, when intensity of growth is high.

A great number of theories have been put forth in order to explain the etiology of the early anemia of prematurity, and the postnatal drop in hemoglobin level in full-term infants. Many authors have maintained that the anemia of prematurity is caused by an insufficiency of the blood-producing organs (Magnusson, Lichtenstein & Nordenson, Küster, Ylppö). However, from the data discussed above we see that premature infants at birth have an extremely active erythrocyte formation, and that their blood-forming organs even in the first months of life are capable of a great production of red cells, when properly stimulated (e.g. by intensive growth, cyanotic heart disease, or by a sufficiently great fall in hemoglobin). The bone marrow studies reported in favor of the theory of a bone marrow insufficiency (Lichtenstein & Nordenson, Gairdner *et al.*) merely reflect the fluctuations in rate of erythrocyte formation discussed above, and do not prove the tenability of the theory.

Gairdner *et al.* have a somewhat different explanation. They maintain: "The early anaemia of premature infants is due mainly to the slow response of erythropoiesis to the stimulus of anaemia." Our findings are hardly compatible with this view. The bone marrow seems to respond rapidly when stimulated by intensive growth. We have also observed that premature infants in connection with spells of asphyxia respond with an almost immediate reticulocytosis, of the same order of magnitude as seen in adults subjected to experimental hypoxia (Seip 1953).

In our opinion it is "normal" and adequate both in premature and full-term infants, when intensity of growth is not particularly great, to have lower hemoglobin values than adults, *because the oxygen consumption*

is—relatively speaking—lower. The main function of the hemoglobin is to transport oxygen to the different organs and tissues. As discussed in detail in an earlier publication (1953), the rate of erythrocyte production normally (within certain limits) is governed by the oxygen supply, or, more correctly, by the relationship between oxygen supply and oxygen consumption. Probably the oxygen tension in a specific blood-regulating center is the decisive factor. When the oxygen supply increases (staying in an atmosphere with higher oxygen content than the air), or the oxygen consumption decreases (hypothyroidism), the demands for red cells are reduced, resulting in a lowered erythropoietic acitivity.

In infancy oxygen consumption, rate of growth not being particularly high, is considerably lower than in older children and adults, in relation to the body surface, which is the most appropriate basis of comparison (see C. A. Smith, *The Physiology of the Newborn Infant*, for a further discussion of this point and for references). In premature infants the oxygen consumption is even lower than in full-term infants, and in direct relationship to their birth weights. The low basal metabolism also manifests itself in their *hypothermia* during the first weeks after birth. In our lowest weight group the body temperature was on an average 34°C during the first week, and rose gradually to 37°C at seven weeks of age. In the group with birth weights of 1500–2000 g the average body temperature was 36°C during the first week, and rose to 37°C in five weeks.

Because of the lower "basic oxygen consumption" in prematures they ordinarily do not need as high hemoglobin levels as full-term infants. However, growth increases the oxygen consumption. We have also seen above that growth increases the rate of erythrocyte formation. This fact is important evidence in favor of our theory that the low hemoglobin levels in premature and full-term infants are related to their oxygen consumption.

To some extent, however, the early anemia of prematurity is also due to the fact that the blood-producing organs in the period of most intensive growth are not able fully to meet the demands. Particularly in the lowest weight group this moment is of considerable importance. The high reticulocyte values in the period from 3–6 to 12–16 weeks of age are a sign of a stronger-than-normal stimulation of the erythropoietic organs, and show that the hemoglobin level in this period is lower than it ideally (considering the babies' oxygen requirements) should have been. These findings, and the iron requirements of premature infants, possibly also the risk of retinal hypoxia, are features suggesting that in the period of most intensive growth one or more blood transfusions may be beneficial, if hemoglobin is low.

The main etiologic factor causing the relatively low hemoglobin and erythrocyte values in premature (and full-term) infants during the first

months of life is in our opinion their relatively low oxygen consumption under "basic" conditions. Intensive growth and a reduced red cell survival are factors of more secondary importance, though not unimportant. The influence of these is greatest in prematures, especially in the lowest weight group.

Stainable Iron in the Bone Marrow of Premature Infants during the First Months of Life

The results for the whole series are given in Fig. 5. Shortly after birth no or very little hemosiderin is present in the bone marrow (grades 0–1). In all cases examined during the next weeks an increase in hemosiderin can be demonstrated, and in some cases to such degrees (grade 4) as are seen in adults in pathological conditions only: infections, pernicious or hemolytic anemia, hemochromatosis. The largest amounts of hemosiderin are found between the fourth and eigth week of life. After this the deposits steadily decrease, until finally no hemosiderin can be demonstrated, 6–12 weeks after birth. In cases where repeated bone marrow studies were done, the course in the individual baby follows the same trend as in the series as a whole. Most of the infants were discharged from the hospital at the age of 8 weeks, and few punctures have been performed between 9 and 12 weeks of age.

Fig. 6 shows the distribution of the results when the infants are grouped according to their birth weights. Because of the relatively small number studied, only two groups are used, with birth weights below and above 1400 g respectively. In the smallest prematures generally less hemosiderin is found, and they are hemosiderin-free earlier (6–8 weeks) than the heavier premature infants (8–12 weeks).

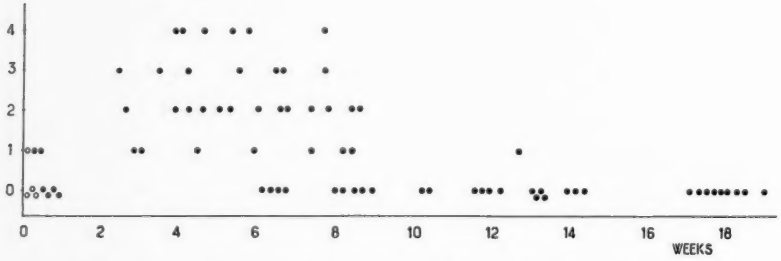

Fig. 5. Bone marrow hemosiderin in premature infants. Results of the whole series.

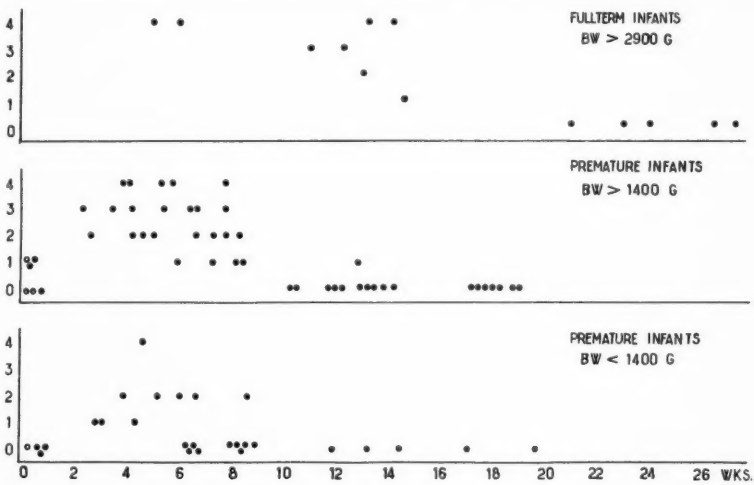

Fig. 6. Bone marrow hemosiderin in fullterm and premature infants grouped according to birth weight.

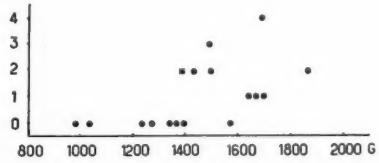

Fig. 7. Bone marrow hemosiderin at the age of 8 weeks plotted against the birth weight.

The same relation to the birth weight is seen from Fig. 7, in which the hemosiderin content of the bone marrow at the age of 8 weeks is plotted against the birth weight of the respective babies. A similar figure at the age of 6 weeks shows the same distribution.

Fig. 6 also shows the results in full-term infants for comparison. In these babies a large amount of hemosiderin can be demonstrated in the bone marrow until the age of 14–16 weeks. After 18–20 weeks the bone marrow is hemosiderin-free in all cases examined.

Six premature infants received iron medication (ferrum reductum 0.1 × 2) from the age of 8–12 weeks. Bone marrow aspirates taken between 12 and 20 weeks of age showed a few hemosiderin deposits (grade 1) in one case, and no stainable iron in the others.

Comments

The method used to demonstrate hemosiderin deposits in the bone marrow is not precisely quantitative, but it gives a reliable index of the iron stores (Finch *et al.*, Hutchinson). These investigators found a close relationship between the findings with this method and the expected pathological changes in iron metabolism. In healthy adults they found a few hemosiderin deposits (grades 1–2), in iron deficiency states no stainable iron (grade 0), and in infections, hemolytic anemia and hemochromatosis increased amounts (grades 3–6).

An important part of the iron stores, the ferritin, is not measured with this method. Shairer & Rechenberger compared the iron content of the liver and spleen with histochemical and quantitative, chemical methods, and they found that a considerable amount was left even when it could not be demonstrated histochemically. Finch *et al.* state as a result of their quantitative studies that hemosiderin and ferritin are used in a parallel manner, and information of hemosiderin will accordingly also inform about the total iron depot. In a review article (1955) they say that a hemosiderin-free bone marrow is the first sign of iron deficiency in adults.

The most important increase in the iron content of the fetus takes place in the last two months of pregnancy as has been shown by Jerlov and Iob & Swansson. The greatest part of this iron is in the hemoglobin, and the increase in the depot organs is small. At birth the iron content of the liver and spleen is small (Widdowson & Spray, Langley). The present study shows that the bone marrow also contains only small amounts of iron during the first days after birth.

Studies on autopsy materials, both with quantitative, chemical investigations (Gladstone, Stearns & McKinley) and histochemical methods (Langley), have shown increasing iron stores during the first weeks of life. The same increase is found in our "normal" premature infants. This verifies that the postnatal siderosis is a normal phenomenon. Langley found that the siderosis remained unchanged until 2–3 months of age both in full-term and premature infants, and decreased slowly after this point. We have found a difference between full-term and premature infants, and also a difference between small and heavier prematures. The cause of this discrepancy may partly be that Langley's figures did not include infants born more than 8 weeks prematurely. Also the fact that infection was the cause of death in most of his cases may account for the increased deposition of iron in the depot organs.

When the results of the reticulocyte counts and those of the iron investigations are compared, we find that the findings verify each other. In the

smallest infants the period of scanty erythropoiesis is short, and an active blood regeneration starts early. As a result of this there will be an increased demand on the iron stores. This coupled with the rapid growth will rapidly empty these stores. The hemosiderin deposits started to decrease before the hemoglobin values had reached their minimum levels, and, in the smallest premature babies, they had even disappeared before this time. In spite of the fall in hemoglobin percentage, the formation of hemoglobin in these infants must be greater than the hemoglobin destruction. Growth is so rapid that the total hemoglobin increases although the hemoglobin percentage is decreasing.

From blood volume studies in premature infants, Schulman *et al.* concluded that the total circulating hemoglobin is decreasing until 6–7 weeks of age and does not reach the same level as at birth until 16 weeks of age. Their opinion is that there can be no iron deficiency before the age of 3–4 months. Blood volume determinations on infants in the first weeks of life must, however, be taken with reservations because the possibilities of errors are numerous. This is also pointed out by Schulman. In our opinion the total circulating hemoglobin in small premature infants reaches the same level as at birth much earlier.

When the amount of iron in one depot organ is taken as a measure for the iron stores in general, the theory is accepted that the depot iron is equally distributed, and that the iron content in different depot organs does not vary independently. This is the most physiological concept and fits well with Hallgren's comparative investigations on the iron content in liver and bone marrow. He found that the amount of iron in these depot organs was equally small when the organism was in a state of iron deficiency, but that the distribution was more uneven when there was a surplus of iron. Finch *et al.* using radioactive iron found certain variations in the distribution of iron in the beginning of a test period. The hemoglobin iron for instance was mostly deposited in the spleen. Under normal conditions, however, even in premature infants, one can assume that the iron of the different depot organs is affected equally. For a further discussion on this problem see Josephs.

It is generally accepted that the late anemia of prematurity is due to iron deficiency and can be cured with iron therapy. Concerning the initial fall in hemoglobin, different investigators have come to different conclusions. Blackfan & Diamond state that iron medication has no influence upon this fall, while Gairdner *et al.* found that the fall in hemoglobin stopped earlier in small infants (birth weights below 1620 g) if given iron from 2–3 weeks of age than if untreated. They advocate giving iron after 3–4 weeks of age to the smallest infants. Reedy *et al.* came to a similar conclusion. On

the other hand, Schulman *et al.* concluded that iron therapy is unnecessary before 3 months of age.

In the present investigations the iron stores have been studied directly, and our results should make it possible to draw valuable conclusions concerning the optimal time to start iron treatment in premature infants. There is, so far, no absolute criterion that the organism is in a state of iron deficiency by a certain amount of hemosiderin in the bone marrow, but one must rely on clinical studies in adults. We have followed the definition of Finch that iron deficiency exists when the bone marrow is hemosiderin-free.

It is not likely that iron medication has any effect on the erythropoiesis, not even stimulating, in the period of increasing iron stores. This agrees with most therapeutic trials. On the other hand one should not wait until a hypochromic anemia has developed. The earliest sign of iron deficiency should mark the latest moment for initiation of iron therapy. In our series this has been between 6 and 8 weeks of age for the smallest premature infants (birth weights below 1400 g) and between 8 and 12 weeks for the heavier ones. The present investigation has also shown that iron medication given orally is not always sufficient to keep the iron depots filled. We feel it must be desirable to start treatment earlier, at the point when the hemosiderin deposits begin to decrease, this indicating that more iron is used than is supplied from hemoglobin destruction and food. Although there is still iron available in the depot organs, iron given therapeutically may be more easily used than the depot iron (Josephs). The smallest premature infants (birth weights below 1400 g) should receive iron from 4–6 weeks of age and the heavier from 6–8 weeks, giving some consideration to the rate of growth in individual babies. This opinion is in agreement with that of Gairdner *et al.*, but disagrees with the statement made by Schulman *et al.* We feel we should warn against starting iron therapy as late as at 3–4 months of age.

It is possible that the most suitable way of giving iron to the very smallest infants will be as blood transfusions, because the blood-forming organs of these infants are working under a great stress on account of the highly intensive growth just at this time. Later one can go on with iron orally. In the heavier premature infants blood transfusion will not be necessary except on special indications.

In full-term infants the hemosiderin deposits disappeared between 4 and 6 months of age. According to the definition used here, they are in a state of iron deficiency from this time. Under normal conditions this deficiency rarely results in a distinct hypochromic anemia, and usually no iron medication is needed. The findings recall the importance of an increased intake of food rich in iron from this time. It is also possible that general symptoms

such as weakness and fatigue may be due to this subclinical (= without anemia) iron deficiency.

As in all blood studies on premature infants one must take into consideration that repeated blood removal even with cutaneous methods as used here, may represent an iron loss which may influence the results. It is therefore not unlikely that iron deficiency may have developed a little earlier in this series than it usually does when no or very little blood is drawn from the babies. We do not, however, feel that this has had any important influence on our results. No difference was found between the group most intensely studied and the others.

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Summary

Erythrocyte production in premature infants was investigated by meticulous reticulocyte studies. The amount of stainable iron was studied in bone marrow preparations, using the Turnbull stain. Intensity of growth, hemoglobin and erythrocyte values were also recorded.

During the first days of life, the rate of erythrocyte formation is high, then rapidly decreases until two weeks of age. This decrease is caused by improved oxygen supply and transient cessation of growth. Then a period of reduced erythropoiesis follows, short (1–2 weeks) in the smallest prematures, longer (3–4 weeks) in the heavier prematures, and longest in full-term infants. It is replaced by a period of intensive, and, in the smallest babies, even highly intensive erythrocyte regeneration.

Growth exerts a stimulating effect on erythropoiesis, probably because it requires an increased oxygen consumption.

The main reason for the low blood values in premature and full-term infants is probably their relatively low oxygen consumption, when intensity of growth is not particularly high. Therefore they do not need the same level of oxygen-carrying hemoglobin as adults. To some extent, however, the anemia is due to the fact that in the period of most rapid growth the blood-forming organs are not able fully to meet the demands.

The pathogenetic factors leading to the postnatal drop in hemoglobin level are (1) growth, (2) increased hemolysis, (3) a transient decrease in erythropoietic activity.

Immediately after birth little or no stainable iron is present in the bone marrow. In the following weeks a marked increase can be demonstrated (up to grades 2–4), the greatest amounts being found between 4 and 8 weeks after birth. After this point iron stores decrease, until finally no hemosiderin can be demonstrated, 6–12 weeks after birth. In the lowest weight group hemosiderin disappears earlier than in the heavier infants. In full-term infants the bone marrow becomes hemosiderin-free at 16–20 weeks of age.

Total hemoglobin begins to increase after 4–6 weeks of age in the smallest prematures This soon leads to a state of iron deficiency (hemosiderin-free bone marrow), and is mainly due to their rapid growth.

The smallest prematures should receive iron from 4–6 weeks and the heavier ones from 6–8 weeks of age, with infants showing the most intensive growth receiving medication somewhat earlier than the others.

Production d'érythrocytes et réserve de fer chez le nourrisson prématuré pendant les premiers mois de la vie.

La production d'érythrocytes a été examinée chez le nourrisson prématuré par une étude méticuleuse des réticulocytes. On a étudié, par le colorant de Turnbull, le taux du fer pouvant être coloré dans la moelle osseuse. La croissance, les taux d'hémoglobine et d'érythrocytes ont aussi été notés. La vitesse de formation des érythrocytes est grande pendant les premiers jours de la vie et diminue alors rapidement jusqu'à l'âge de deux semaines. La diminution est provoquée par un meilleur approvisionnement en oxygène et un arrêt momentané de la croissance. Suit alors une période d'érythropoièse réduite qui est courte (1–2 semaines) chez les très petits prématurés, plus longue (3–4 semaines) chez les plus lourds, et la plus longue chez les nourrissons nés à terme. Elle est remplacée par une période de régénération intense, même très intense chez les nourrissons les plus petits, des érythrocytes. La croissance exerce un effet stimulant sur l'érythropoièse, probablement à cause de la nécessité d'une plus forte consommation d'oxygène. La consommation relativement basse d'oxygène, quand la croissance n'est pas particulièrement forte, est probablement la cause principale des valeurs basses dans le sang des prématurés et des nourrissons nés à terme. Ils n'ont pas besoin du même taux d'hémoglobine transportant l'oxygène que les adultes. L'anémie est cependant jusqu'à un certain point dûe au fait que les organes hémopoiétiques ne peuvent pas satisfaire complètement les demandes pendant la période de croissance la plus rapide. Les facteurs de la pathogénèse qui conduisent à la baisse post-natale de l'hémoglobine sont (1) la croissance, (2) l'augmentation de l'hémolyse, (3) une réduction passagère de l'activité érythropoiétique. Il n'y a dans la moelle osseuse, immédiatement après la naissance, que peu ou pas de fer pouvant être coloré. On peut montrer, pendant les semaines suivantes, une forte augmentation (jusqu'aux degrés 2–4), les plus grandes valeurs étant trouvées entre les 4 et 8 semaines après la naissance. Après ce moment les réserves de fer diminuent, jusqu'à ce qu'on ne trouve finalement plus d'hémosidérine 6 à 12 semaines après la naissance. L'hémosidérine disparait plus précocement chez le groupe d'enfants pesant peu que chez les nourrissons plus lourds. Chez les nourrissons nés à terme la moelle osseuse ne contient plus d'hémosidérine à l'âge de 16 à 20 semaines. L'hémoglobine totale commence à augmenter chez les plus petits prématurés après l'âge de 4–6 semaines. Ceci conduit rapidement à un état de carence en fer (moelle osseuse sans hémosidérine) et est surtout provoqué par leur croissance rapide. Les plus petits prématurés devront recevoir de fer dès l'âge de 4–6 semaines et les plus lourds dès l'âge de 6–8 semaines; les nourrissons ayant une croissance plus rapide recevront le médicament un peu plus tôt que les autres.

Produktion von Erythrocyten und die Eisenreserve bei frühgeborenen Säuglingen während der ersten Lebensmonate.

Die Erythrocytenproduktion wurde bei frühgeborenen Säuglingen durch ein genaues Studium der Retikulocyten untersucht. Man untersuchte mit der Turnbull-

färbung die im Knochenmark färbbare Eisenmenge. Die Zunahme der Hämoglobinmenge und der Erythrocyten wurde ebenfalls notiert. Das Vermögen zur Erythrocytenbildung ist gross während der ersten Lebenstage, um dann bis zum Alter von 2 Wochen schnell abzunehmen. Die Verminderung wird verursacht durch eine bessere Sauerstoffausnutzung und einen vorübergehenden Aufenthalt des Wachstums. Es tritt eine Periode der reduzierten Erythropoese ein, die bei den sehr kleinen Frühgeburten kurz ist (1–2 Wochen), bei den grösseren länger (3–4 Wochen) und bei den rechtzeitig geborenen Säuglingen am längsten. Sie wird abgelöst von einer Periode der intensiven Erythrocytenregeneration, die selbst bei sehr kleinen Säuglingen äusserst intensiv ist. Das Wachstum hat, wahrscheinlich auf Grund des stärkeren Sauerstoffverbrauches, einen stimulierenden Effekt auf die Erythropoese. Der relativ niedrige Sauerstoffverbrauch bei nicht zu starkem Wachstum ist wahrscheinlich die Hauptursache der niedrigen Werte im Blute der Frühgeburten und der rechtzeitig geborenen Säuglinge. Sie benötigen nicht die gleiche sauerstofftransportierende Hämoglobinmenge wie die Erwachsenen. Die Anämie ist dagegen bis zu einem gewissen Grade dadurch verursacht, dass die hämopoetischen Organe nicht völlig die Forderungen der schnellen Wachstumsperiode zufriedenstellen können. Die pathogenetischen Faktoren, welche die niedrigen postnatalen Hämoglobinwerte verursachen, sind: 1. das Wachstum, 2. die vermehrte Hämolyse, 3. eine vorübergehende Verminderung der hämopoetischen Aktivitet. Unmittelbar nach der Geburt gibt es im Knochenmark wenig oder kein färbbares Eisen. Während der folgenden Wochen kann man eine starke Vermehrung finden (bis zu 2–4 Graden); die höchsten Werte findet man zwischen der 4. und 8. Woche nach der Geburt. Danach nehmen die Eisenreserven ab, bis endlich 6 bis 12 Wochen nach der Geburt das Knochenmark kein Eisen mehr enthält. Das Hämoglobin verschwindet schneller bei der Gruppe der wenig wiegenden Kinder als bei schwereren Säuglingen. Bei rechtzeitig geborenen Säuglingen enthält das Knochenmark im Alter von 16 bis 20 Wochen kein Hämosiderin mehr. Bei den ganz kleinen Frühgeburten beginnt das Totalhämoglobin im Alter von 4–6 Wochen zu steigen. Dieses führt schnell zu einem Zustand des Eisenmangels (Knochenmark ohne Hämosiderin), der sicherlich durch das schnelle Wachstum hervorgerufen wird. Die sehr kleinen Frühgeborenen müssen Eisen im Alter von 4–6 Wochen zugeführt bekommen, die grösseren im Alter von 6–8 Wochen. Sehr schnell wachsende Säuglinge benötigen eine etwas grössere Menge als andere.

Producción de eritrocitos y reserva de hierro en el nacido de parto prematuro, durante los primeros meses de vida.

Se ha investigado la producción de eritrocitos en el prematuro, mediante un estudio minucioso de los reticulocitos. Se ha estudiado, por medio del colorante de Turnbull, la cantidad de hierro que peude ser coloreada en la médula ósea. También fué observado el aumento de la cantidad de hemoglobina y de eritrocitos. La rapidez con que se producen los eritrocitos es grande durante los primeros días de vida, disminuyendo luego rápidamente hasta la edad de dos semanas. La disminución tiene por causa un mejor aprovisionamiento de oxígeno y una detención momentánea del crecimiento. Sigue luego un período de eritropoesis reducida, el cual es corto (1 a 2 semanas) en los muy pequeños prematuros, y más largo (3 a 4 semanas) en los de más peso, siendo el más largo en los nacidos en debido tiempo. A este período sucede otro de regeneración intensa de los eritrocitos, muy intensa incluso en los niños más pequeños. El crecimiento ejerce una influencia estimulante sobre la eritropoesis, a causa probablemente de la necesidad de un consumo mayor de oxígeno. El consumo relativamente escaso

de oxígeno cuando el crecimiento no es particularmente fuerte, es probablemente la causa principal de los valores bajos en la sangre de los prematuros y los recien nacidos. Estos no necesitan la misma cantidad de hemoglobina que los adultos para transportar el oxígeno. La anemia, sin embargo, es debida hasta cierto punto al hecho de que los órganos hemopoéticos no pueden satisfacer plenamente las demandas durante el período más rápido del crecimiento. Los factores de la patogenia que conducen a la disminución posnatal de la hemoglobina son: 1) el crecimiento, 2) el aumento de la hemolisis, 3) una reducción pasajera de la actividad eritropoética. En la médula ósea no hay, inmediatamente después del nacimiento, más que poco o nada de hierro que pueda ser coloreado. Se puede mostrar, durante las semanas siguientes, un considerable aumento (hasta los grados 2–4), encontrándose los valores más altos entre las 4 y 8 semanas después del nacimiento. Después de este momento, las reservas de hierro disminuyen hasta que, finalmente, no se encuentra ya más hemosiderina 6 a 12 semanas después del nacimiento. La hemosiderina desaparece más pronto en el grupo de niños de poco peso que en los niños de más peso. En los niños nacidos en debido tiempo, la médula ósea no contiene ya más hemosiderina a la edad de 16 a 20 semanas. La hemoglobina total comienza a aumentar en los más pequeños nacidos de parto prematuro después de la edad de 4–6 semanas. Esto conduce rápidamente a un estado de carencia de hierro (médula ósea sin hemosiderina), producida probablemente por su rápido crecimiento. A los más pequeños nacidos de parto prematuro se les deberá dar hierro desde la edad de 4–6 semanas, y a los de más peso des de laedad de 6–8 semanas; a los niños cuyo crecimiento sea más rápido se les dará el medicamento en cantidades un poco más grandes.

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Les Hématomes Sous-Duraux

Etude expérimentale

Par FRANÇOIS GIRARD

La découverte de collections sanguines ou séro-hématiques situées à la face interne de la dure-mère et se développant parfois dans l'espace sous-dural est un fait observé avec une relative fréquence, surtout chez le nourrisson.

L'origine de cet épanchement est le plus souvent obscure; c'est à ce problème que nous nous sommes spécialement attachés.

Rappel anatomique

L'accord n'est pas entièrement réalisé sur la description des enveloppes cérébrales. On admet généralement le schéma de Weed ci-dessous.

On notera qu'entre dure-mère et arachnoïde s'étend l'espace sous-dural. C'est un espace virtuel entourant l'ensemble du système cérébro-spinal. Il est traversé par des vaisseaux : les veines se rendant du cortex cérébral aux sinus. Il est également traversé par les villosités de Pacchionni (Weed). On n'y retrouve normalement aucun liquide.

L'arachnoïde qui le borde en dedans est toujours intacte en cas d'hématome.

La dure-mère, au contraire, est toujours atteinte et, pour beaucoup d'auteurs, les lésions se développeraient à l'intérieur même de ses feuillets.

— Classiquement, on distingue dans cette formation, un feuillet interne et un feuillet externe.

— Mais d'autres plans de clivage plus ou moins artificiels ont pû être reconnus (jusqu'à sept pour Melnikow-Raswendenkow).

— Il est intéressant de préciser l'existence d'un certain nombre de réseaux vasculaires : 4 principaux pour Pfeiffer, un seul important pour Hannah. Cependant, ces deux auteurs insistent l'un et l'autre sur la présence à la partie la plus profonde de la dure mère, et séparé de l'espace sous-dural par une couche très mince de une ou deux assises de cellules fibreuses, d'un réseau capillaire extrêmement dense et d'une très grande finesse (difficultés de coloration histologique des parois). Ces capillaires peuvent être le siège de fortes dilatations et, pour ces auteurs, ce réseau compenserait par sa plus ou moins grande réplétion les variations de volume du cerveau. Expérimentalement, Hannah a pu constater que le sang citraté injecté dans la dure-mère se rassemblait dans ce réseau. C'est enfin à la fase profonde de la dure-mère et à ce même niveau que pour de nombreux auteurs se produirait l'hémorragie (de Morsier, Debré, Lelong et al.).

Nous verrons qu'expérimentalement les lésions obtenues se situent principalement dans cette zone de capillaires profonds.

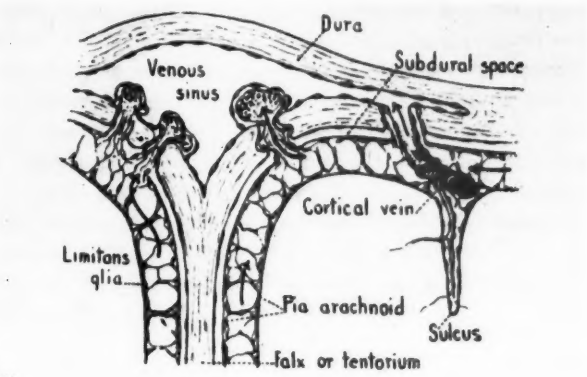

Fig. 1. Les enveloppes cérébrales (D'après Weed, *J. med. Res.*, 1914, *31:57-92.*)

Mécanisme de l'hémorragie

Deux problèmes se posent dans l'étude de l'origine des hématomes sous-duraux : Il convient d'étudier, d'une part, l'origine de l'hémorragie en précisant son mécanisme et en localisant son siège, d'autre part, la constitution de ce qui est le plus souvent appelé l'hématome sous-dural.

C'est le mécanisme de l'hémorragie que nous envisagerons plus particulièrement ici.

Les diverses hypothèses

Pendant longtemps, l'origine hémorragique des lésions constatées a été mise en doute (Charcot & Vulpian; Virchow). Actuellement, la plupart des auteurs considère que l'hémorragie est primitive, la dure-mère s'organisant secondairement (Baillarget, Jores).

Quelque soit le facteur étiologique retrouvé, l'origine de l'hémorragie semble bien due à une rupture vasculaire : la composition du liquide de l'hématome est, tout au moins au début, très voisine de celle du sang.

Mais pour expliquer le mécanisme de cette rupture vasculaire, de nombreuses hypothèses ont été formulées.

1. Une origine traumatique néo-natale a pu être mise en évidence dans certains cas (Gröntoft). Ce traumatisme peut être invoqué même lorsque le début des troubles ne s'est manifesté que plusieurs mois après la naissance. Mais bien souvent, cette naissance s'est déroulée sans le moindre incident. Le traumatisme accidentel est toujours possible chez l'enfant. La ponction lombaire a été accusée. Nous verrons que, au cours de nos expériences, des

prélèvements répétés et importants de L.C.R. ont été incapables de provoquer la moindre hémorragie sous-durale.

2. Une altération primitive de la dure-mère capable de fragiliser les vaisseaux a été retenue. Elle peut être congénitale (angiomes, hématomes sous-duraux et fractures multiples) ou inflammatoire (syphilis, tuberculose, infection aigue des espaces sous-arachnoïdiens).

3. Les carences étaient pour Finkelstein un facteur important dans la génèse de l'hémorragie. L'hypoprothrombinémie entre dans ce cadre (Lelong).

4. Un mécanisme de sensibilisation de la dure-mère a même été avancé (Zehnder).

Parmi les différents mécanismes envisagés, seul le traumatisme est capable d'entraîner effectivement une rupture vasculaire. Les autres mécanismes hypothétiques ne peuvent jouer qu'un rôle favorisant. Cependant, souvent ce traumatisme ne peut pas être mis en évidence. Cette hypothèse explique mal

— le siège le plus souvent intra-dural et bilatéral de la lésion,

— la présence à côté de l'hématome organisé, de nombreuses hémorragies pétéchiales à la face profonde de la dure-mère,

— l'identité des lésions quelque soit le facteur étiologique retrouvé.

C'est pourquoi une autre hypothèse a été envisagée qui semble s'accorder mieux avec les faits : L'hémorragie sous-durale serait en rapport avec une diminution de la pression intra-cranienne accompagnant un collapsus cérébral.

Le collapsus est souvent retrouvé au cours des interventions pour des hématomes sous-duraux d'origine variée : traumatismes accidentels ou opératoires, insolations, états infectieux divers. Et depuis Leriche et Cl. Vincent, de nombreux auteurs ont insisté sur l'importance de « ramener le cerveau à la paroi » dans le traitement de ces lésions. Pour certains même (Cl. Vincent, Mahoudeau, Le Beau, Guillaume & Oeconomos, Chavany & Pertuiset, Lazorthes et al.), cet affaissement du cerveau ne serait pas dû à la compression provoquée par l'hématome. Au contraire, ce collapsus serait primitif et l'hémorragie ne serait que sa conséquence.

Le mécanisme de l'hémorragie peut être imaginé de la manière suivante : La diminution du volume du cerveau entraînerait à l'intérieur du crâne une pression négative. La boîte cranienne ayant un volume relativement fixe, le collapsus cérébral serait compensé par un afflux sanguin (Wegelin) qui ira dilater les différents systèmes vasculaires de la dure-mère et en particulier la couche capillaire la plus interne décrite par Pfeiffer et par Hannah. La pression négative régnant à ce moment dans l'espace sous-dural entraîne-

rait un étirement — soit des vaisseaux traversant en pont cet espace, soit des capillaires de la face profonde de la dure-mère — et provoquerait leur rupture. Partant de cette lésion primitive, l'hématome s'organiserait progressivement.

Il est difficile de faire la preuve directe de la dilatation capillaire au moment du collapsus. Par contre, indirectement, l'étude du débit sanguin intra-cranien n'est pas contre cette hypothèse (Shenkin). D'un autre côté, la mise sous pression négative de l'espace sous-dural peut être prouvée aisément par la technique de la pneumographie sous-durale faite soit à crâne ouvert (Penfield), soit le crâne intact (Eichhorn & Moschik de Reya, Jönnis & Loew, Mayer & Moschik de Reya).

Expérimentation

C'est donc en partant de l'hypothèse d'une hypotension intra-cranienne à l'origine des hématomes sous-duraux que nous avons tenté de provoquer les hémorragies de la dure-mère susceptibles de se collecter dans l'espace sous-dural.

De nombreux expérimentateurs (Marie et al., Putnam et al., Cohn, Koch, Zendher) ont tenté de provoquer l'hématome en attaquant directement la dure-mère et en y injectant divers produits.

Nous avons écarté systématiquement toute agression au niveau du crâne : le seul fait d'ouvrir la boîte cranienne étant susceptible d'entraîner des modifications incontrôlables de la physiologie cérébrale.

Dans une première série d'expériences, nous avons tenté de provoquer l'affaissement du cerveau par soustraction de liquide céphalo-rachidien.

Des essais ont été tentés chez le chien, le cobaye et le lapin. Mais l'animal choisi a été le jeune chat de quatre semaines environ en raison de la facilité de la ponction sous-occipitale sous anesthésie générale légère et en raison du bon développement de son système ventriculaire.

Il a été vérifié par encéphalographie gazeuse que les ventricules pouvaient être vidés complètement de leur liquide.[1] Onze animaux ont subi un ou plusieurs prélèvements de L.C.R. L'animal était couché, on laissait s'écouler le L.C.R. jusqu'à tarissement spontané (1 à 2 cc). Il a été procédé parfois à 6 ponctions, 6 jours de suite et au maximum à 3 séries de 6 ponctions, séparées entre elles par une semaine de repos. Le prélèvement du cerveau après sacrifice de l'animal par anesthésie à l'éther et ouverture de la carotide a été effectué par voie extradurale et fixé au formol.

[1] Nous remercions à ce propos le Dr. Lefèvre et le Dr. Kamo-Gami de leur précieux concours.

Aucune modification macroscopique de la dure-mère n'a pu être observée.

La raison de cet échec peut être expliquée par les considérations suivantes :

— Déplétion insuffisante des ventricules. (Cependant, la quantité de L.C.R. prélevée était égale à celle remplacée par de l'air pour obtenir une ventriculographie complète.)

— L'activité des plexus choroïdes aurait été capable de compenser la perte de liquide. (On sait que les hypo-tensions intra-craniennes par perte traumatique de L.C.R. ne surviennent que lorsque la perte est importante et continue.)

— Et surtout le fait que la déplétion ventriculaire ne provoque pas un collapsus cérébral vrai avec diminution du volume de la substance cérébrale elle-même (Weed, Cl. Vincent et ses élèves).

Dans une deuxième série d'expériences, l'injection d'un soluté de ClNa hypertonique a été utilisé.

Weed & Mac Kibben, dans une série d'études sur les variations de la pression du liquide céphalo-rachidien ont montré que l'injection de sérum salé hypertonique provoquait chez le chat une baisse de la pression du L.C.R. jusqu'à des valeurs nulles et parfois négatives, à ce moment, on observe un collapsus cérébral marqué. Leurs études anatomiques précises avec fixation du cerveau et de ses enveloppes in situ ont montré que cette diminution de volume était dûe, non seulement à la déplétion ventriculaire, mais aussi aux changements de volume de la substance cérébrale elle-même.

Technique

On injecte par voie intra-péritonéale une solution de ClNa à 20 % à la dose de 1,5 cc pour 100 g de poids. L'injection est généralement bien supportée, cependant la mort de l'animal a été parfois observée dans les 12 heures qui ont suivi l'injection. Dans les autres cas, l'animal a été sacrifié de 6 à 24 h. après l'injection par la technique décrite plus haut.

Résultats

A l'ouverture du crâne, un collapsus cérébral, souvent important, a été observé (cerveau à 2 ou 3 mm de l'os — 6 cas). Dans certains cas même, il n'était pas nécessaire d'utiliser la rugine pour séparer la dure-mère du périoste. Dans tous les cas, il a été constaté une extravasation sanguine intra-cranienne.

Deux séries d'animaux peuvent être distinguées. Chez 10 chats âgés de 3 à 5 semaines, il a été constaté 9 hémorragies de la dure-mère et une hémorragie mixte, d'un côté intra-durale, de l'autre sous-durale. Chez 5 chats âgés de 3 à 7 jours, on a pu noter 2 hémorragies de la dure-mère et 3 hémorragies sous-arachnoïdiennes ou mixtes.

Fig. 2.

Dans tous les cas d'hémorragie de la dure-mère, la lésion était visible à l'œil nu. Elle était faite de flaques de 1 à 5 mm de diamètre, parfois confluentes en plages plus importantes. Avant l'ouverture des enveloppes, ces lésions étaient vues en transparence à travers la dure-mère. Lorsqu'on sépare la dure-mère du cerveau, elles restent accolées à la dure-mère et se développent à sa face profonde. Il est difficile de voir sous cet angle à l'œil nu la membrane qui limite l'hémorragie en dedans. Le cerveau sous-jacent et la méninge molle sont d'aspect normal.

La lésion siégeait au niveau des pôles occipitaux (lésion bilatérale : 7 cas), au niveau de la dure-mère du cervelet (3 cas), au niveau de la faux du cerveau (1 cas), dans la région pariétale (1 cas).

L'étude des coupes au microscope a confirmé les constatations macroscopiques, elle a permis de préciser les points suivants :

— l'intégrité de la méninge molle, sauf dans les cas des chats nouveau-nés où alors l'hémorragie méningée était évidente;

— le siège de l'hémorragie.

Dans tous les cas, sauf un, l'hémorragie était intra-durale; elle intéressait

Fig. 3.

la partie la plus profonde de la dure-mère et n'était séparée de l'espace sous-dural que par une assise de 1 ou 2 couches de cellules fibreuses de la dure-mère.

La photographie, Fig. 4, montre l'ensemble de la lésion observée. La photo, Fig. 5, objective au fort grossissement la situation de l'hémorragie.

Ces constatations sont en accord avec les observations anatomiques de nombreux auteurs : Barthez & Rillet parlaient d'hématomes de la dure-mère; cette conception était reprise par Ehrenfest, Debré et al., de Morsier, Lelong et al., Caldéra, qui avaient constaté sur des examens anatomiques post mortem que l'hématome était intra-dural et non sous-dural comme il est classique de le dire (Trotter, Leary et al., Ingraham et al.).

A la lumière de ces faits, le point de départ de l'hémorragie semble bien le réseau capillaire profond de la dure-mère et non pas les veines traversant en pont l'espace sous-dural.

Il est possible cependant que l'hémorragie se propage dans l'espace sous-dural en rompant la fine assise cellulaire qui limite en dedans l'hématome. L'examen anatomique du chat nº 39 nous semble démonstratif à cet égard : macroscopiquement, hémorragie sous-durale bilatérale de la région pariétale; microscopiquement, à gauche (Fig. 6) infiltration de la face profonde de la

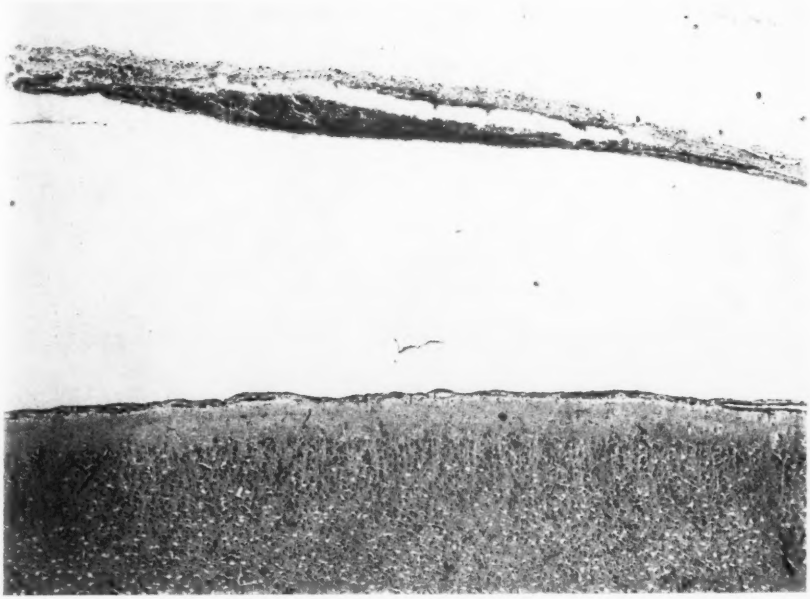

Fig. 4.

dure-mère, l'espace sous-dural est libre. A droite (Fig. 7), hémorragie sous-durale vraie avec dure-mère et arachnoïde intactes à ce niveau.

Si donc l'effusion de sang dans l'espace sous-dural est possible, il ne semble pas qu'elle soit responsable de ce qu'il a été convenu d'appeler l'hématome sous-dural. Les expérimentateurs (Marie et al., Putnam et al.) qui ont injecté du sang dans l'espace sous-dural n'ont pas pu obtenir l'hématome organisé. Au cours des interventions neuro-chirurgicales, une certaine quantité de sang est laissée nécessairement dans l'espace, un épanchement organisé secondaire est exceptionnel (de Morsier).

Discussion des résultats

Les lésions observées ne semblent pas être des artéfacts. Elles n'ont pas été retrouvées chez les 11 animaux de la première série d'expériences. Ultérieurement, trois autres animaux intacts ont été sacrifiés suivant la technique standard : aucune lésion ne fut retrouvée (Fig. 8).

Cependant, on pourrait objecter :

— que le mode de prélèvement du cerveau par voie extra-durale pourrait dilacérer les capillaires engorgés et provoquer une apparence d'hémorragie ;

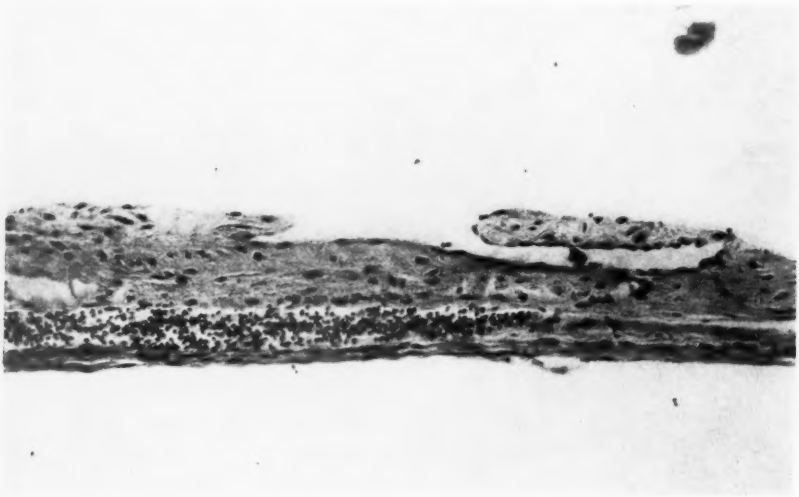

Fig. 5.

— que l'état général des animaux était précaire au moment du sacrifice;

— que les lésions auraient pu se produire dans les derniers instants de la vie et que l'on ne peut englober dans la même série les animaux morts spontanément aux animaux sacrifiés;

— que les conditions de l'hypertonie était par trop extra-physiologiques et que les lésions obtenues n'étaient que la traduction d'une intoxication aigue par le chlorure de sodium.

Pour éliminer ces causes d'erreurs, les vérifications suivantes ont été faites. Dans un cas, la dure-mère a été laissée adhérente à la tente du cervelet qui est ossifiée chez le chat. Elle n'en a été séparée qu'après fixation au formol. La lésion était toujours la même. Dans deux cas, seules des ouvertures ont été faites dans la boîte cranienne et l'ensemble a été fixé trois semaines dans le formol. Des hémorragies existaient dans des zones qui n'avaient pas été découvertes au préalable.

Le sacrifice d'un animal, en poussant l'anesthésie à l'éther jusqu'à l'asphyxie a montré une vaso-dilatation plus nette que chez les témoins sacrifiés après ouverture de la carotide mais pas d'hémorragie de la dure-mère.

Dans une dernière série d'expériences, il a été tenté de conserver les animaux après l'injection de sérum hypertonique. Dans 3 cas sur 5 cette rééquilibration a été possible. On a pu alors constater un début d'organisation de

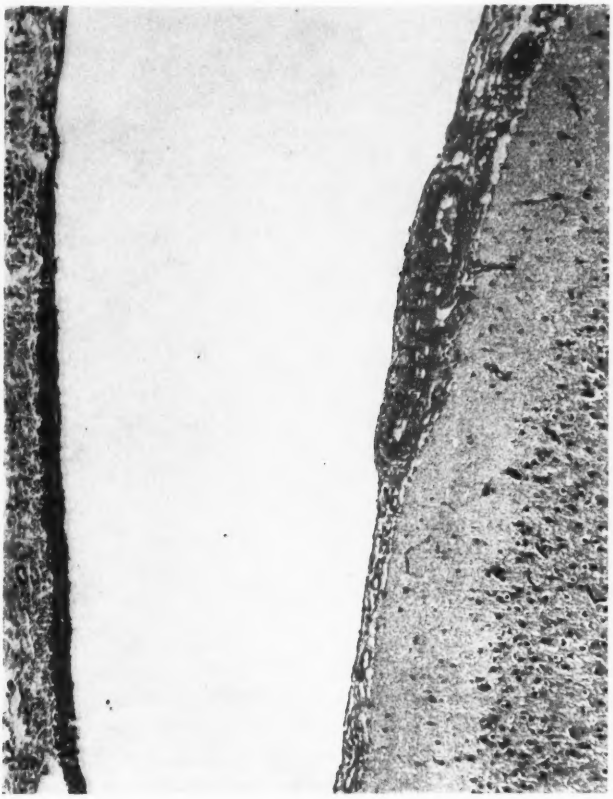

Fig. 6.

la lésion attestant que celle-ci n'était pas contemporaine de la mort de l'animal.

Certes, en plus du collapsus cérébral, l'injection de sérum hypertonique peut provoquer d'autres perturbations susceptibles de favoriser l'hémorragie: déshydratation intense, perturbations importantes de l'équilibre des électrolytes. Il a été constaté en effet dans 6 cas des suffusions hémorragiques ailleurs : purpura au niveau du péritoine, congestion vasculaire sans infarcissement de certains lobes pulmonaires et d'un rein, dilatation capillaire sous la capsule du foie. Dans les autres cas, d'hémorragie de la dure-mère, aucune autre lésion hémorragique n'a pu être retrouvée, même par l'histologie.

Nous avons pu cependant dans trois cas contrôler chimiquement le degré

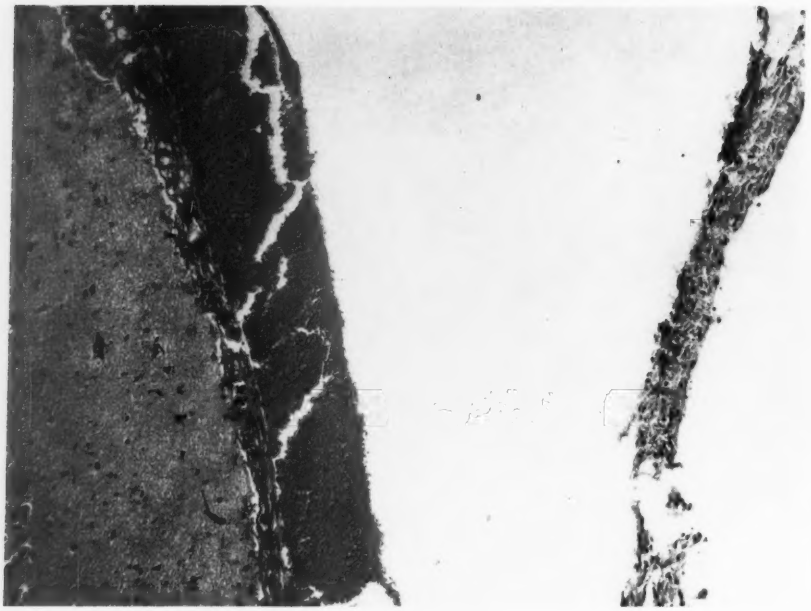

Fig. 7.

de l'hyperélectrolytémie. Les chiffres oscillent pour le sodium autour de 200 mEq/L et pour le chlore autour de 170 mEq/L. Ces chiffres sont très élevés, mais ils peuvent être approchés et même dépassés au cours des déshydratations du nourrisson (Chaptal et al., Finberg & Harrison, un cas personnel). Si donc, les conditions de production de ces hémorragies de la dure-mère sont anormales on ne peut pas dire quelles soient sans rapport avec les conditions réalisées au cours de certains états pathologiques.

On peut donc retenir, de ces diverses expériences, un fait intéressant : L'injection de sérum salé hypertonique qui entraîne un collapsus cérébral est susceptible de provoquer une extravasation sanguine intra-cranienne et cette extravasation se situe précisément dans la couche la plus profonde de la dure-mère, provoquant des lésions comparables à certaines images de la pathologie humaine.

Constitution de l'hématome chronique

Le mécanisme de l'entretien et de reproduction de l'hématome a été également l'objet de très nombreux travaux. Il est certain que des phénomènes de pression osmotique jouent un rôle important (Zollinger & Gross,

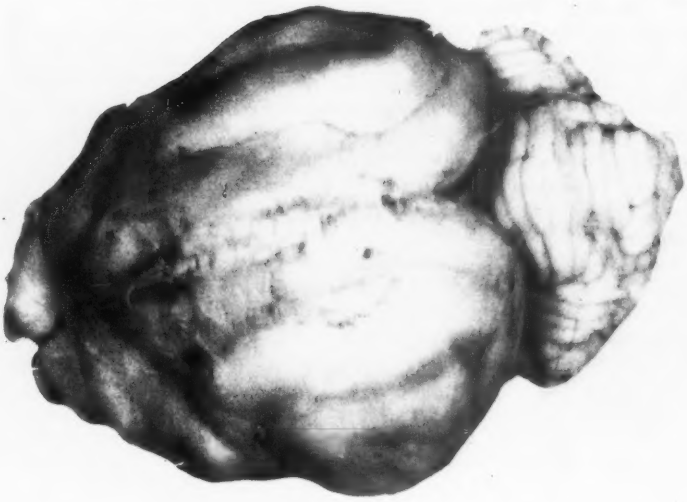

Fig. 8.

Fischer & de Morsier). Il semble cependant que le saignement persiste pendant toute l'évolution (Giltin).

Dans l'ensemble, nos expériences n'ont pas été poursuivies au-delà de 24 h. Dans un travail en cours, il est tenté de conserver les animaux pour observer si, partant de l'hémorragie de la dure-mère décrite plus haut, un épanchement chronique se constitue. Sur les cinq premiers animaux expérimentés, trois ont survécu. Des signes d'organisation des lésions ont pu être décelés, mais le nombre de cas est trop faible pour qu'il puisse en être fait état ici.

Conclusions

A la lumière des faits exposés ci-dessus, il semble que le collapsus cérébral soit capable de provoquer une extravasation sanguine au niveau de la dure-mère. Or, dans de nombreuses circonstances de la vie du nourrisson, un collapsus cérébral peut être observé.

Au cours des syndromes de déshydratation, non seulement une fontanelle creuse est observée, mais parfois un véritable chevauchement des sutures est noté. La P.L. ne ramène parfois aucun liquide témoignant de l'hypotension intra-cranienne. L'hypertonie plasmatique et en particulier l'hypernatrémie est le plus souvent accentuée et on sait cliniquement l'importance des signes neurologiques au cours de tels états : troubles de la conscience, convulsions, troubles moteurs. Des hématomes de la dure-

mère ont pu être constatés au décours d'états toxiques sévères (Caldéra, de Pavi et al.). Dans de nombreuses maladies infectieuses de l'enfance un collapsus cérébral peut être retrouvé. Morice, envisageant le problème d'un point de vue neuro-chirurgical a colligé dans sa thèse de nombreux cas. Pour lui, le syndrome paleur-hyperthermi serait la traduction clinique d'un collapsus.

Le collapsus cérébral est également possible au cours des méningites. Dès 1906 Netter signalait l'existence de méningites à nuque molle, Ribadeau-Dumas & Siguie décrivaient les formes paralytiques de la méningite du nourrisson. Debré, Thieffry & Doumic en 1947 présentaient sept cas de collapsus ventriculaire au cours de méningites. Il n'est pas impossible que ces troubles de l'hydratation cérébrale observés soient à l'origine des épanchements dure-mériens constatés avec une fréquence croissante depuis que la guérison de la plupart des méningites peut être obtenue.

Le traumatisme lui-même peut, par l'intermédiaire d'un collapsus cérébral secondaire, être à l'origine de l'hématome sans qu'il y ait eu de rupture vasculaire primitive.

Les tumeurs du lobe temporal avec hernie temporale qui comprimen la partie supérieure du tronc cérébral, s'accompagnent parfois d'une hypotension intra-cranienne (Le Beau & Houdart).

L'étude clinique des cas d'hématomes sous-duraux dits spontanés permet, dans certains cas, de mettre en évidence un affaissement cérébral : déshydratation, malnutrition, atrophie cérébrale dégénérative, méningite. Dans d'autres cas, l'enquête étiologique est tout à fait muette. Si donc, l'hypothèse d'un collapsus est susceptible d'apporter une explication à un certain nombre de cas, elle ne les explique vraisemblablement pas tous.

Une telle étude ne nous a cependant pas paru dénuée d'intérêt, car elle peut comporter une sanction à la fois prophylactique et thérapeutique : Rechercher chez l'enfant malade le moindre signe de collapsus cérébral, en particulier au cours des méningites et le traiter (la méthode préconisée par Leriche, réhydratation isotonique massive, semble la plus favorable). Veiller constamment dans la conduite du traitement d'un hématome de la dure-mère à maintenir un état d'hydratation cérébral satisfaisant.

Subdural Hematoma. Experimental Study.

Intravenous injection of hypertonic saline in dogs produces cerebral collapse. The collapse may in turn provoke an intracranial hemorrhage. This becomes localized at the deepest layer of the dura and gives rise to lesions that are comparable to certain morbid states in human beings. Cerebral collapse may be observed in many circumstances of an infant's life: dehydration syndromes, severe toxic states, infectious diseases, meningitis, direct or indirect trauma. In all these cases spontaneous subdural hematoma may develop and the existence of cerebral shrinkage can be proved by clinical study in some of them. In other cases, the etiological interview is negative and therefore the hypothesis of a collapse probably does not explain every case of subdural hematoma.

Subdurale Hämatome. Eine experimentelle Studie.

Die Injektion von hypertoner Kochsalzlösung bewirkt bei Hunden einen cerebralen Kollaps und führt eine intracranielle Blutung herbei, die genau in der tiefsten Schicht der Dura mater gelegen ist und Schädigungen herbeiführt, die denen der menschlichen Pathologie vergleichbar sind. Beim Säugling kann unter zahlreichen Bedingungen ein cerebraler Kollaps beobachtet werden: im Verlauf des Dehydrationssyndroms, bei

schweren toxischen Zuständen, bei zahlreichen Infektionskrankheiten des Kindesalters, im Verlauf von Meningitiden, bei direkten oder indirekten Traumen. Bei allen diesen Zuständen können sich spontan subdurale Hämatome entwickeln und die klinische Untersuchung erlaubt, in gewissen Fällen eine cerebrale Beteiligung mit Bestimmtheit anzunehmen; in anderen Fällen ist der ätiologische Faktor völlig unklar und die Hypothese eines Kollapses ist nicht bei allen Fällen von subduralem Hämatom befriedigend.

Los hematomas subdurales. Estudio experimental.

La inyección de suero salino hipertónico en el perro provoca un colapso cerebral que es suceptible de provicar una extravasación sanguínea intracraneana que se sitúa precisamente en la capa mas profunda de la duramadre provocando lesiones comparables a ciertos cuadros de la patología humana. En numerosas circunstancias de la vida del lactante se puede observer un colapso cerebral: duranta el síndrome de deshidratación, en estados tóxicos severos, numerosas enfermedades infecciosas, meningitis y traumatismos directos o indirectos. En todos estos estados pueden producirse hematomas subdurales permitiendo el estudio clínico poner en evidencia un colapso cerebral. En otros casos, la encuesta etiológica es totalmente muda y la hipótesis de un colapso no explica claramente la etiología del hematoma.

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Aus der Kinderklinik der Palacký-Universität, Olomouc, Tschechoslowakei

Noch einmal zur schnellen Realimentation bei schwerer Säuglingsdyspepsie und Toxikose

von M. JADRNÍČEK und A. MORES

Die auf Grund unserer Mitteilung von E. Freudenberg (*Acta pædiat., 44:* 579, 1955) veröffentlichte Replik erfordert noch einige kurzgefasste Anmerkungen.

1. Es überrascht uns durchaus nicht, dass E. Freudenberg mit den von uns gezogenen Schlussfolgerungen nicht übereinstimmt, ebenso wie er den von Chung und Viščorová i. J. 1949 vertretenen Ansichten nicht zustimmte; es ist jedoch zu ersehen, dass die von ihm gemachten Einsprüche sichtlich schwächer werden, so wie auch manche seiner früher angeführten Gründe im Laufe der Zeit an Überzeugungskraft verloren haben. Wir führen z. B. an: wenn die 10% betragende Sterblichkeit schnell alimentierter Säuglinge i. J. 1949 zum ernsten Vorwurf gemacht wurde, weisen unsere 2,5% ganz eindeutig darauf hin, dass die Sterblichkeitsursache eine andere war: Chung und Viščorová standen keine so wirksamen Antibiotica, wie derzeit uns, zur Verfügung und es verdient vor allem betont zu werden, dass auf ihrem Arbeitsplatze die Methode der parenteralen Rehydratation damals noch nicht so ausgearbeitet war, wie dies heutzutage auf jedem Arbeitsplatze selbstverständlich ist.

2. Eine Diskussion, ob unsere Kranken zu den intoxizierten gezählt oder nicht gezählt werden sollen, kann nicht geführt werden, der Autor muss die Möglichkeit zugeben, auch wenn die angeführten Kranken zufällig keine Temperatur aufwiesen. Dieses nicht völlig unbedingte Symptom der Toxikose wurde jedoch bei unseren anderen Kranken, die in einer früheren, das gleiche Thema behandelnden Mitteilung (*Čsl. pediatrie, 10:* 124, 1955) von uns angeführt wurden, verzeichnet. Sie wurden genau so schnell wie die Kranken ohne Temperatur realimentiert, wobei die Schnelligkeit des Gesundungsvorganges die gleiche blieb. Beweis dafür, dass die Anzahl der Intoxikationen durch keinen begünstigenden, diagnostischen Masstab vergrössert wurde, ist ihre bei uns verzeichnete Frequenz: im Jahre 1952 betrug die Zahl 21 von 854 im Alter bis zu einem Jahr aufgenommener Säuglinge, i. J. 1953 bloss 6 von 931.

3. In unserer Mitteilung wurde nicht bloss die Literatur, die sich mit der schnellen Realimentation befasst, sondern auch jene, welche einige unserer Thesen bekräftigt, erwähnt. Die von Mann u. Mitarb. veröffentlichte Arbeit wurde zur Unterstützung der von uns vertretenen Ansicht über die Notwendigkeit der vollkommenen Rehydratation bei der Behandlung der Durchfälle angeführt, da uns keine Möglichkeit zur Verfügung stand, die Originalarbeiten von Mariott und Finkelstein zu beschaffen. Die Arbeit von Keefe ist eine zusammenfassende Abhandlung über die Behandlung der Säuglingsdurchfälle, einschliesslich der epidemischen und der Neugeborenendurchfälle, bei denen neben Äpfeln auch vollwertige Nahrung, sogar bis 150 Kal./Kg täglich, gereicht wurde.

Es ist uns unbekannt, ob die von Mitchell u. Mitarb. behandelten Kranken an Hitze litten, bei unseren schnell Realimentierten war jedoch primäre, wenn auch nicht immer bakteriologisch genau definierbare Darminfektion vorhanden. Es gab bei ihnen auch keine parenteralen Ursachen, welche derzeit, wenn sie überhaupt existieren, vernachlässigt werden können.

4. Wir hegen keine Zweifel betreffs der anatomischen und funktionellen Störungen an den Verdauungsorganen des an Durchfall erkrankten Kindes, welche auch in der verringerten Fähigkeit, die gereichte Nahrung auszunützen, ihren Widerhall finden. Wir sind uns dieser Tatsache bewusst und reichen deshalb manchmal nach vollkommener Rehydratation eine leichter verdauliche Nahrung (Buttermilch oder saure Milch, jedoch keine Eiweissmilch, obzwar wir diese geben würden, wenn wir sie hätten), doch drängen wir nichts auf, sondern bieten bloss an. Das Kind trinkt so viel wie es verdauen kann. Falls die Mengen in den ersten Tagen gering sind und deshalb neue Dehydratation infolge andauernder Durchfälle droht, werden parenteral Salzlösungen gereicht, denn gute Toleranz — wir wiederholen das bereits in der Originalarbeit von uns Ausgeführte — kann bloss durch vollkommene Rehydratation verbürgt werden.

5. Unser Interesse bezieht sich weder auf die Anzahl noch auf die Ausgiebigkeit der Stühle, ebenso wie dies z. B. bei der Behandlung der an Typhus erkrankten Personen keine Rolle spielt; denn wir behandeln den Kranken, keinesfalls seinen Stuhl.

6. Durch schnelle Realimentation wird nicht bloss die somatische Dystrophierung, die bei kurz andauerndem Hungern übrigens nicht eintreten muss, verhindert, sondern es wird auch die Widerstandskraft des Organismus gehoben und dadurch die Möglichkeit der Relapse verringert. Von R. Dubos aus der Rockefeller-Stiftung in New York wurde im Tierversuch der Beweis erbracht, dass die Resistenz gegen bakterielle Infektionen sichtlich absinkt, falls die Tiere vorher 24 bis 30 Stunden lang dem Fasten ausgesetzt werden.

7. Wir sind uns bewusst, dass auch in neuen Lehrbüchern stets die alte,

langsame Methode der Realimentation angegeben wird; gerade diese Tatsache veranlasste uns, die auf Grund einer völlig unterschiedlichen Methode von uns gewonnenen, sehr guten Erfahrungen zu veröffentlichen.

8. Begreiflicherweise werden bei uns alle Säuglinge mit Durchfall auch weiterhin schnell realimentiert; in den Jahren 1954 und 1955 konnten sogar noch weitaus bessere Ergebnisse als in den Jahren 1952 und 1953 erzielt werden. In den Jahren 1952 und 1953 betrug die gesamte Sterblichkeit bei beiden Krankheitsformen 2,5%, i. J. 1954 nur mehr 1% und i. J. 1955 bereits 0%; zu ergänzen wäre, dass im Verlaufe der ersten zwei Jahre noch insgesamt 27 Toxikosen vorkamen, davon 4 mit tödlichem Ausgang, während in den folgenden 2 Jahren nur 10 Toxikosen und kein Todesfall verzeichnet wurden. Die ganzen 4 Jahre hindurch schwankte die Anzahl der an unserer Klinik jährlich aufgenommenen Säuglinge zwischen 830 bis 930. Das immer seltenere Auftreten schwerer Durchfälle bei Säuglingen weist darauf hin, dass die Infektion — und nicht diätetische Missgriffe — ihre Hauptursache seit jeher gewesen ist und dass deshalb auch ihre diätetische Behandlung keine so grosse Bedeutung hat, wie man voraussetzte und wie bisher noch von vielen angenommen wird.

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Histological Changes of the Pyloric Myenteric Plexus in Infantile Pyloric Stenosis

Studies on Surgical Biopsy Specimens[1]

by O. STEINICKE NIELSEN

Within recent years several authors have advocated the view that infantile pyloric stenosis is due to disturbances of the autonomic nervous system of the stomach (Knauar, Bendix & Necheles, Belding). Assessment of the results of these workers requires a knowledge of the normal courses and the normal function of the autonomic nerves of the stomach. A fair agreement has gradually been reached regarding the innervation of the stomach. The stomach receives sympathetic fibres from the thoraco-lumbar part; these are interrupted in the coeliac ganglion, from which the postganglionic fibres continue to the stomach itself. In addition, the stomach is supplied with parasympathetic fibres from both vagal nerves. These nerves are interrupted peripherally in the stomach in Auerbach's and Meissner's plexi, from which postganglionic nerves lead to the gastric muscles (Mitchell, White *et al.*). The parasympathetic innervation of the pyloric portion differs from that of the remaining stomach, the pylorus being innervated separately through the so-called hepatic branch of the anterior (right) vagus which gives off fibres to the pylorus. The normal structure and the microscopic picture of the intramuscular ganglia of the stomach have been elucidated by Hill, who found the cells to be classifiable into two types according to the length of the dendrons.

While there is fair agreement as to the course of the innervation, opinion is still divided with regard to the motility of the stomach. It is a current view that the peristalsis in the body of the stomach is decreased by sympathetic stimulation, whereas vagal stimulation has an increasing effect. However, animal experiments have shown that the effect of vagal stimulation depends on the mechanical state of the stomach as well as on the intensity

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of the stimulation (McCrea *et al.*, McCrea & McSwiney). The same writers have also shown that the motor function of the pyloric portion is independent of that of the remaining stomach, and that the response of the pyloric musculature to vagal and sympathetic stimulation, respectively, differs from that of the body of the stomach. Even though these facts have not yet been sufficiently clarified, there is no doubt that severe degenerative changes of the intramuscular ganglia in the pyloric portion will bring about an abnormal neurogenic impulse through the vagus, resulting in alterations in the function of the pylorus. Such degenerative changes have been demonstrated by Herbst in two infants who died with pyloric stenosis. Similar changes of the intramuscular ganglion cells were found and described by Raia in biopsy specimens from pyloric musculature in a child with pyloric stenosis. In these cases the ganglion cell changes were characterized by severe, irreversible degeneration with atrophic cells and proliferation of the glial tissue. Alarotu & Christensen and Belding & Kernohan made similar observations by examining the stomachs of 29 and 9 infants, respectively, who died of congenital pyloric stenosis. In the latter work, which is very comprehensive, the authors claim to have shown, in addition to the stated ganglion cell degeneration confined to the pyloric area, a reduced number of ganglion cells in the pyloric portion both in children with pyloric stenosis and in adults with cured congenital pyloric stenosis.

The above-mentioned examinations were made exclusively on post mortem material. In the present paper an account is given of ganglion cell examinations carried out on muscular biopsy specimens taken from infants during operation for pyloric stensosis.

Present Investigations

Material

Biopsy specimens for histological examination were obtained from pyloric musculature of 15 infants submitted to pylorotomy owing to congenital pyloric stenosis within the period of March 1954 to March 1955. Ten of the infants had been admitted to the Paediatric Department, the County Hospital of Copenhagen, Gentofte (KASG), and operated on in Department N of this hospital, while five had been admitted to the Children's Hospital, Fuglebakken, and operated on in the Municipal Hospital of Copenhagen, Department V.[1]. All the infants had presented the signs typical of pyloric stenosis, i.e. explosive vomiting, loss of weight, and gastric peristaltis, and in 14 cases a distinct pyloric tumour had been palpable before the operation. The birth weights

[1] I wish to thank P. Bræstrup, M.D., chief of the Paediatric Department, the KASG, for permission to collect biopsy specimens and for access to the case records. Further, I wish to thank Ib Andersen, M.D., chief of the Surgical Department N, the KASG, and Kjæld Trautner, Deputy Superintendent of the Surgical Department V, the Municipal Hospital of Copenhagen, for removing biopsy specimens from pyloric muscles.

ranged from 2500 to 4000 g. There were 11 boys and 4 girls. Only one infant had prio to operation been submitted to treatment with eumydrine drops for 9 days. The aver age age at appearance of clinical signs was 4 and at operation $6\frac{1}{2}$ weeks. The age in cidence is shown in Table 1.

The biopsy specimens were usually $1 \times 1 \times 4$ mm in size. They were fixed in 4 pe cent formalin immediately after having been excised. Serial sections were made, an more than 100 preparations of each specimen were examined.

Between August 1954 and June 1955, a control material of stomachs from eigh children, six girls and two boys, who died in the Children's Hospital, Fuglebakken between the ages of 6 hours and 12 days was collected for histological examination. The birth weights and causes of death of these children are stated in Table 2. The stomachs were fixed in 4 per cent formalin as soon as definite signs of death were present, and sections for histological examination were cut from the duodenum, the pyloric portion, and from the middle of the body of the stomach.

The surgical material as well as the control material were submitted to haematoxylin–eosin staining, van Gieson's connective tissue staining and Einarson's gallocyanine staining (Einarson 1932). (6). The sections for microscopy were prepared in the Psychiatric Laboratory, the University Hospital, Copenhagen, and the histological examinations were carried out with expert aid from Erna Christensen, M.D., neuropathologist, to whom I am greatly indebted for this aid.

Results

The analysis of the biopsy specimens comprises exclusively the morphological and structural conditions of the intramuscular ganglia. The variations in size of the specimens as well as in the site of excision from the pyloric musculature preclude an exact evaluation of the total number of ganglia, as done by Belding & Kernohan who found a reduced number in the pyloric portion in proportion to that found in normal infants of the same age-class. The number of ganglion cells in Table 1 therefore refers only to the finding of many or few cells in the biopsy specimen concerned. It follows that the observation of pathological cell forms is most conclusive in the cases where many ganglion cells have been found. In the histological analysis, rendered in Table 1, a distinction has been made between normal (chromoneutral and chromophobic), chromatolytic and atrophic ganglion cells. The quantitative distribution of these cell types is indicated by figures, the sum of which makes 4. By this procedure a uniform assessment of the histological picture is obtained in spite of the varying numbers of ganglion cells found in the biopsy specimens.

The examinations here reported revealed severe degenerative changes in the intramuscular ganglion cells. The degree and type of degeneration varied from one biopsy specimen to another, as well as within the same specimen. In certain cases the degeneration was dominated by atrophic cells (Fig. 1), while in others the chromatolysis prevailed (Fig. 2). In the cases of chromatolytic degeneration, the individual ganglion cells had undergone pronounced changes with loss of Nissl bodies. The cells were large, pale, of a loose structure, with irregular nuclear membrane. Often only shadows of cells were seen as a precursor of cell disintegration. In the atrophic form the cells

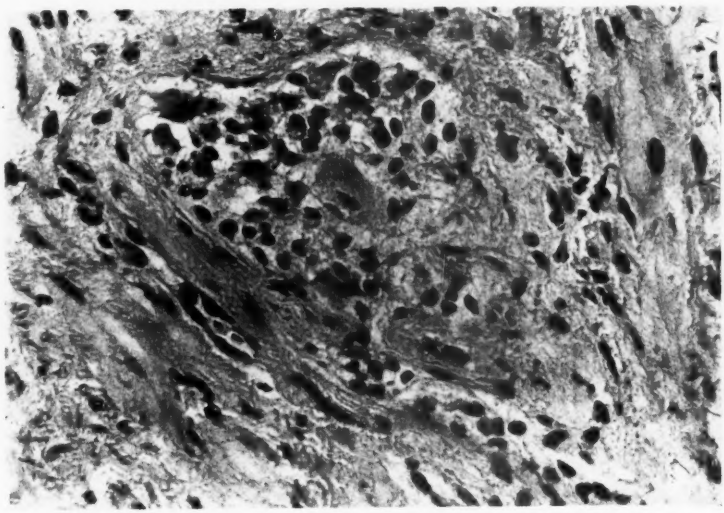

Fig. 1. (No. 468). Degenerative changes of a myenteric ganglion Auerbachii in a biopsy specimen of pyloric muscle from an infant operated for congenital pyloric stenosis at the age of 6 weeks. The majority of the ganglion cells were atrophic and pyknotic, a few, however, chromatolytic and swollen. Rather pronounced glial proliferation in the upper half of the ganglion. Gallocyanine × 400.

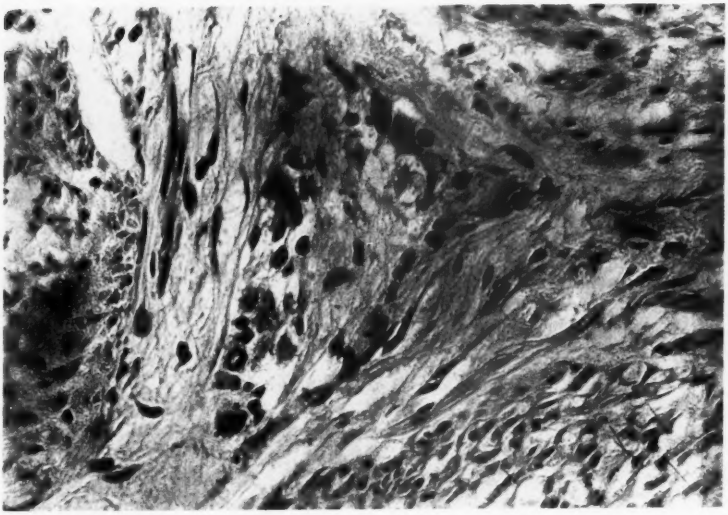

Fig. 2. (No. 470). Degenerative changes of a myenteric ganglion Auerbachii in a biopsy specimen of pyloric muscle from an infant operated for congenital pyloric stenosis at the age of 9 weeks. The ganglion cells were in the main highly chromatolytic, a few cells in a state of disintegration. In addition, a few atrophic cells were found. No proliferation of glial tissue. Gallocyanine × 400.

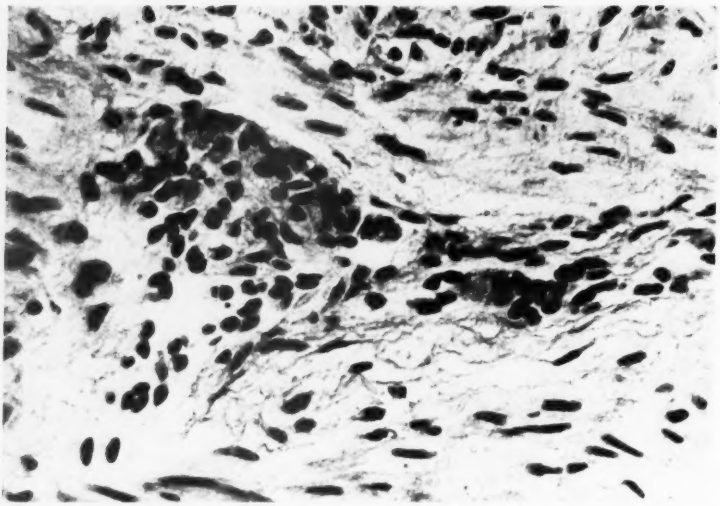

Fig. 3. (No. 498). Degenerative changes of a myenteric ganglion Auerbachii in a biopsy specimen of pyloric muscle from an infant operated for congenital pyloric stenosis at the age of 6 weeks. The ganglion cells were chromatolytic or atrophic; the picture is characterized by the pronounced proliferation of the glial tissue. Gallocyanine × 400.

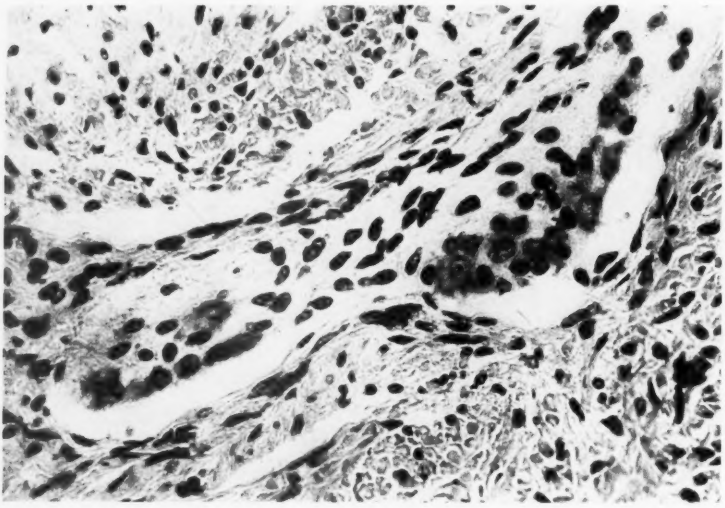

Fig. 4 (No. 525). Normal myenteric ganglion from the pyloric portion of an infant who died from cerebral haemorrhage at 2 days of age. The ganglion is divided by a vessel into two sections. The ganglion cells are normal, without proliferation of the glial tissue. Gallocyanine × 400.

TABLE 1

Histological analysis of the intramuscular ganglion cells in biopsy specimens of pyloric muscles from 15 infants operated on for congenital pyloric stenosis.

"Number of ganglion cells" indicates the rough number in the biopsy specimen concerned. Thus, + represents few, + + several, and + + + many cells. The ganglion cells found are divided into three groups according to their structural state. The quantitative distribution of these three cell types is indicated by figures the sum of which makes 4. Concerning the glial proliferation, I, II, and III refer to mild, moderate and pronounced proliferation respectively.

No.	Sex	Age in weeks at		Number of ggl. cells	Ganglion cells			Glial proliferation
		onset of signs	operation		Normal	Chromatolyt.	Atrophic	
504	M	3	4	+	1	2	1	I
499	M	4	5	+ + +	—	1	3	III
468	F	5	6	+ + +	—	1	3	III
500	M	6	7	+	—	2	2	II
554	M	6	7	+ +	—	1	3	II
453	M	2	4	+	—	1	3	I
534	M	3	5	+ + +	—	2	2	III
463	M	5	7	+	—	1	3	—
509	F	2	5	+	—	2	2	II
498	F	3	6	+ +	—	1	3	III
482	M	3	6	+ +	1	2	1	I
553	M	4	7	+	—	2	2	I
491	F	7	10	+ + +	—	2	2	II
540	M	3	7	+	—	1	3	II
470	M	3	9	+ + +	—	1	3	III

were excessively shrunken with a highly pyknotic nucleus. In addition to these changes of the ganglion cells, a more or less pronounced proliferation of the glial tissue, manifesting itself by a greatly increased number of oval glial nuclei (Fig. 3), was found in all cases. The degree of this proliferation in the individual biopsy specimens is also shown in Table 1.

The histological examination of the control material comprised, in addition to the intramuscular ganglion cells, the mucous membranes, the appearance of which was assessed with a view to the degree of a possible autolysis. The mucous membrane was found slightly chipped off in few sections only, and pronounced autolysis was not seen anywhere. Sections from the eight infants of the control group were examined from the duodenum, pylorus and body of the stomach. The ganglion cells in the different sections from the same patient differed but little in appearance and have therefore been assessed collectively for each infant, as seen in Table 2. The numbers of

TABLE 2

Histological analysis of the intramuscular ganglion cells in stomachs from eigh infants who died without clinical signs of congenital pyloric stenosis.

The ganglion cells are divided into three groups according to their structural state. Th quantitative distribution of these cell types is indicated by figures the sum of which makes 4 The degree of proliferation of glial tissue is indicated by − (= no) and + (= mild) proliferation

No.	Sex	Age in days	Birth weight in g	Cause of death	Ganglion cells			Glial proliferation
					Normal	Autolytic	Chromatolyt.	
539	F	¼	750	Atelectasis, asphyxia, prematurity	1	2	1	−
483	F	¼	1800	Cerebral hemorrhage, prematurity	1	2	1	−
523	F	2	4300	Cerebral hemorrhage, atelectasis	1	2	1	−
568	F	3	2330	Scleroderma, prematurity	1	2	1	+
481	M	4	3900	Adrenal hemorrhage	2	2	—	−
530	F	6	1540	Atelectasis, pneumonia, prematurity	3	1	—	−
501	F	10	2800	Congenital heart disease	1	2	1	+
567	M	12	2090	Meningitis, prematurity	2	2	—	−

ganglion cells demonstrated in the eight analysed cases were fairly equal. In proportion to the cells of the biopsy material, those of the control material varied in the individual sections between "some" and "many". The ganglion cells have been classified, according to their appearance, into (1) normal, (2) autolytically changed, and (3) chromatolytic. The proportional distribution within these three groups is indicated by the figures 1, 2, 3, 4. The results of the control examinations were that the ganglion cells were normal or slightly autolytically changed at most (Fig. 4). These autolytic changes manifested themselves by oedema of the ganglia themselves, and by the large, swollen, oedematous, pale individual ganglion cells which often had an eccentrically located nucleus. Table 2 shows further that proliferation of the glial tissue was not demonstrated in the control material. The microscopic picture of the intramuscular ganglia can thus be regarded as normal in the control group, the changes observed being due exclusively to unavoidable postmortal processes.

Discussion and Conclusions

The histological examinations of 15 biopsy specimens from infants operated for congenital pyloric stenosis revealed severe irreversible degenerative changes of the intramuscular ganglion cells. No such changes were observed in a control material. Though five of the controls were prematures and the age incidence in the two groups was very unequal, we may, in view of the pronounced pathological changes demonstrated in the biopsy specimens, be justified in regarding these changes as characteristic of congenital pyloric stenosis. The fact, that the changes found here in fresh surgical specimens were practically identical with those demonstrated by other workers in post mortem preparations (Herbst, Alarotu & Christensen, Belding & Kernohan) is further evidence in support of this hypothesis.

Various theories have been advanced about the aetiology and pathogenesis of congenital pyloric stenosis, and especially about the role of the ganglion cell degeneration. According to one of these theories, the pathological state of the autonomic nerve tracts of the pyloric portion is to be regarded as the most important factor in the development of congenital pyloric stenosis. The interruption of the parasympathetic impulses through the vagal nerves results in spasms of the pyloric muscles, which respond by hypertrophy, thus giving rise to the characteristic pyloric tumour. A few facts militate against this theory, however. If the ganglion cell degeneration is present at birth, one should expect the pyloric spasms, the clinical signs, to occur immediately after birth. If, on the other hand, the degeneration only develops during the first two weeks of the infants life, it is difficult to account for the fact that a well-developed muscular hypertrophy is present already a few days after the occurrence of clinical signs, and that in a few instances a pronounced thickening of the pyloric musculature has been demonstrated a few days after birth (Rinvik, Meeker & De Nicola). Donovan even noticed hypertrophy of the pyloric muscles in a 7 months old foetus. The fact that pyloric hypertrophy has been demonstrated roentgenologically in infants without clinical signs also speaks against the view of ganglion cell degeneration as the primary factor (Wallgren, Lewis). Finally, it is difficult to explain, on the basis of this theory, the peculiar spontaneous cure of the disease after a few months.

According to another theory, which seems to me a more plausible one, the intramuscular ganglion cell degeneration is a consequence of the pyloric hypertrophy, which must then be regarded as the main cause of the disease. The primary hypertrophy causes obstruction in the pyloric portion. To overcome the increased resistance the peristalsis will be intensified, and this

will gradually tire out the motor nerve tracts of the pyloric muscles, resulting in gradual degeneration of the intramuscular ganglion cells. The presence of muscular hypertrophy in a few infants shortly after birth, or even in foetal life, can easily be explained on the basis of this theory. The experience that clinical signs as a rule do not occur until several weeks after birth may be because pyloric spasms start only with beginning ganglion cell degeneration. This may also explain the spontaneous disappearance of the signs at the stage of total degeneration, as the possibility of muscular contractions (spasms) then will have ceased to exist. The clinical cure of the disease by means of pylorotomy may be explained on a purely mechanical basis; cutting of the circular muscle fibres prevents the spasms from continuing.

The question, whether differences in the severity of the ganglion cell degeneration, dependent on the duration of the clinical signs, could be demonstrated, has been investigated, but as can be seen from Table 1, no such differences were demonstrable.

Our present knowledge does not permit us to decide whether any of the stated theories is correct. This does not prevent us from assessing the significance of the intramuscular ganglion cell degeneration for the course of the disease. Both previous workers and the author have found the degeneration to be irreversible, characterized by atrophic ganglion cells as well as excessive glial proliferation. It must therefore be supposed to be demonstrable throughout life in these patients. In this connection I want to report the case of a boy who was operated on for pyloric stenosis at the age of 1 month and was free from symptoms, until he died from pneumonia at the age of 10 months. The stomach of this infant revealed pronounced intramuscular ganglion cell degeneration with atrophic cells as well as glial proliferation corresponding exactly to the findings in the biopsy specimens. In addition, a persisting pronounced hypertrophy of the pyloric muscles was seen. Belding & Kernohan have made similar observations in five adult patients, who all had suffered from pyloric stenosis in early infancy and had been treated by gastro-enterostomy. In contrast to the findings of Belding & Kernohan, in the author's case here reported, the typical ganglion cell degeneration was not limited to the pyloric portion but involved the whole stomach and the uppermost part of the duodenum.

If the ganglion cell degeneration in the pyloric portion persists, this also explains why the majority of adults submitted in early infancy to medical treatment for pyloric stenosis continue to present roentgenographic changes in the prepyloric area (Steinicke Nielsen & Roelsgaard). The changes found must be regarded as disturbances of motility due to impaired or completely abolished neurogenic function. The question therefore suggests itself whether

total degeneration can be avoided by early surgical treatment. If so, it may be possible to prevent permanent disturbances of motility and also to reduce the risk of development of gastric ulcer in individuals with cured congenital pyloric stenosis (Bendix & Necheles, Steinicke Nielsen).

Summary

Biopsy specimens of pyloric muscles from 15 young infants operated on for congenital pyloric stenosis have been submitted to histological examination. This revealed severe irreversible degeneration of the intramuscular ganglion cells in all cases. These cells were found to be highly chromatolytic or atrophic, and the ganglia presented varying degrees of glial proliferation. The stomachs of eight infants dead without clinical signs of pyloric stenosis were submitted to similar histological examination for control. Here the intramuscular ganglion cells were normal.

The significance of this ganglion cell degeneration for the aetiology and pathogenesis of congenital pyloric stenosis has been discussed together with the significance of the roentgenologically demonstrable disturbances of motility in the prepyloric area of individuals with cured congenital pyloric stenosis.

Changements histologiques du plexus myentérique du pylore dans la sténose pylorique du nourrisson. Etude de spécimens obtenus par biopsie chirurgicale.

On a soumis à l'examen histologique des spécimens, obtenus par biopsie, du muscle pylorique provenant de 15 jeunes nourrissons opérés de sténose congénitale du pylore. On a trouvé ainsi dans tous les cas une dégénérescence grave irréversible des cellules ganglionnaires intramusculaires. Ces cellules montraient une forte chromatolyse ou atrophie et les ganglions présentaient des degrés variables de prolifération gliale. Les estomacs de huit nourrissons décédés sans signes cliniques de sténose du pylore ont été soumis pour contrôle à un examen histologique semblable. Les cellules ganglionnaires intramusculaires étaient normales ici. La signification de cette dégénérescence des cellules ganglionnaires pour l'étiologie et la pathogénèse de la sténose congénitale du pylore a été discutée, ainsi que la signification des troubles de la motilité de la région prépylorique, trouvés à l'examen radiologique, chez des individus guéris de sténose congénitale du pylore.

Histologische Veränderungen im Myenterialplexus des Pylorus bei Pylorusstenose von Säuglingen. Eine Studie von durch chirurgische Biopsie gewonnenen Präparaten

Das Material dieser histologischen Untersuchung wurde durch Biopsie des Musculus pylorus von 15 Säuglingen erhalten, die wegen einer Pylorusstenose zur Operation kamen. Man hat in allen Fällen eine schwere irreversible Degeneration der intramuskulären Ganglienzellen gefunden. Diese Zellen zeigten eine schwere Chromatolyse oder Atrophie und die Ganglien wiesen verschiedene Grade von Gliaproliferation auf. Die Mägen von acht ohne klinische Zeichen von Pylorusstenose gestorbenen Säuglingen wurden zu Kontrollzwecken der gleichen histologischen Untersuchung unterzogen. Die intramuskulären Ganglienzellen waren in diesen Fällen normal. Die Bedeutung dieser Ganglienzelldegeneration für die Ätiologie und die Pathogenese der

Pylorusstenose wird diskutiert, ebenso wie die Bedeutung der Motilitätsstörung der Präpylorusregion, die man röntgenologisch bei von Pylorusstenose geheilten Individuen finden kann.

Alteraciones histológicas del plexo myentérico del píloro en la estenosis pilórica del lactante. Estudio de especímenes obtenidos por biopsia quirúrgica.

Han sido objeto de examen histológico especímenes, obtenidos por biopsia, del músculo pilórico de 15 lactantes operados de estenosis congénita del píloro. Se ha descubierto en todos los casos una degeneración grave irreversible de las células ganglionares intramusculares. Estas células mostraban una fuerte cromatolisis o atrofia, y los ganglios presentaban diferentes grados de proliferación glial. Los estómagos de ocho de los lactantes fallecidos sin signos clínicos de estenosis del píloro han sido sometidos como control a un examen histológico similar. El estado de las células ganglionares intramusculares era normal en estos casos. Se ha discutido la importancia de esta degeneración de las células ganglionares para la etiología y la patogenia de la estenosis congénita del píloro, así como la importancia de los trastornos de la motilidad de la región prepilórica hallados en el examen radiológico en los individuos curados de estenosis congénita del píloro.

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Local Inhibition of the Tuberculin Reaction after Repeated Testing of BCG-vaccinated Subjects

by R. BERFENSTAM and K.-E. FICHTELIUS

BCG vaccination and regular tuberculin testing have become increasingly common, and in Sweden a new generation is growing up that has been BCG-vaccinated within a few days of birth, and subsequently subjected to regular tuberculin testing at child-welfare clinics and during the school years. The frequently-tested young individual may later choose an occupation in which regular medical examination, including tuberculin testing, is considered essential, and in which it is required that the subject show a positive tuberculin reaction. It is a common observation, however, that certain persons giving a strongly positive tuberculin reaction after BCG vaccination gradually become tuberculin-negative, and remain so in spite of the fact that BCG vaccination has been repeated several times. In such cases the requirement of a positive tuberculin reaction may constitute a hindrance to training, and thus influence the young person's choice of occupation.

It is therefore of great importance to establish the cause of the fading of the positive reaction to tuberculin. It has been assumed that the tuberculin allergy following BCG vaccination is neither as strong nor of such duration as that following natural immunization. A fundamental question, however, is whether the disappearance of the tuberculin allergy is a general phenomenon, or whether the change from positive to negative reaction occurs only locally and is connected with the frequent tests which are carried out routinely on the arm.

Many investigations have been carried out to compare the result of tuberculin testing at the same site as that of a former test with the result of testing at a new site. A review is given by Wasz-Höckert. The intervals between two tests have varied from 4 to 137 days. Most investigators have found that among healthy subjects, both natural reactors and BCG-vaccinated ones, retesting at the same site produced a heightened reaction. Furthermore, the subsequent reaction also appears more quickly (Weiss, Björnstad Honkanen, Wasz-Höckert, Edwards & Magnus). Thus the difference between

a repeated test and the control is greatest during the first 24 hours (Weiss, Edwards & Magnus).

Under other circumstances a weaker reaction or no reaction may be obtained. Borok & Pick gave intradermal injections of increasing doses of tuberculin within a strictly limited area in man. (The conditions under which they carried out the experiments are not described in detail, but they seem to have performed the injections once weekly over a period of 3–4 months.) They found that the tuberculin testing subsequently gave negative results within this area, but positive results within a symmetrical control area. In an article published in the *Lancet* (1955), Heaf describes briefly an investigation carried out by Bowen. She retested tuberculin-positive subjects on the same arm after one year, which is the longest interval we have encountered in the literature. After the first year the reversion rate was 10 per cent for the fresh vaccine. At the end of the second year the corresponding figure was 20 per cent. Because of the high reversion rate, Bowen retested on both arms and found that one year after vaccination some previously positve children were negative on the arm used and positive on the other. When retesting was done on the opposite arm to that on which tuberculin testing had previously been performed the reversion rate after one year fell to about 2 per cent. Nothing is said about the time at which the reaction was read, or its appearance during the first 24 hours after injection of tuberculin.

As far as we know, *no comparative investigation of the behaviour of the tuberculin reaction at sites used a number of times during the course of several years and the reaction at sites never before employed* has been published. An investigation of this nature is now described.

The tests were performed on a series of student nurses aged 20–25 years, all of whom had been BCG-vaccinated one or more times (with the possible exception of a few, see Tables 1 and 2), and who had been tuberculin tested on the arm 10–20 times before. A mixture of human and bovine tuberculin,[1] in dilutions of 1/1000 and 1/100, was used. The tuberculin was injected intracutaneously in the usual manner, on the outer surfaces of both arm and thigh.

Experiment I.—The first group consisted of 39 students, all negative to 1 mg of tuberculin on one of the arms.

The average observation period was 2 years, the number of previous tests during this time being 9. When the negative reaction[2] on the arm was read, or one or two days later, 1 mg of tuberculin was injected into the skin of the lateral surface of the right thigh, and this reaction was read 72 hours later. The findings are given in Table 1.

[1] From the State Bacteriological Laboratory, Stockholm.

[2] A negative reaction means that after 72 hours the area of infiltration was less than 10 × 10 mm. A positive reaction is one in which the area of infiltration measured 10 × 10 mm or more.

TABLE 1

Thirty-nine student nurses negative to *1.0 mg of tuberculin* on the arm, tested wit the same dose on the right thigh.

The numbers after the initials indicate the total numbers of tuberculin tests carried ou on the arms during the period of observation. BCG vaccinations and tuberculin tests a noted in chronological order in each case. A −, negative arm-reaction; A +, positive arm reaction; T +, positive thigh-reaction; T −, negative thigh-reaction.

Case	No. tuberculin tests	BCG vacc. and tuberculin tests (in chronol. order)
I. S.	8	BCG? A + A + A + A − A − T +
I.J.	11	BCG A + A + A + A − A − BCG A − T −
M. N.	5	BCG A + A − A − T +
C. G.	4	BCG BCG A − A − T +
G. H.	4	BCG A + A − T −
G. S.	4	BCG BCG BCG A − T −
B. W.	10	BCG A + A + A + A + A − T −
M. R.	8	BCG? A − A − BCG A − T −
M. S.	10	BCG? A + A + A + A − T +
L. S.	8	BCG A + A + A − BCG A − T +
B. L.	12	BCG A + A + A − BCG A + A + A − T +
L. S.	8	BCG A + A + A − T −
G. J.	9	BCG A + A − A − BCG A − T +
L. H.	8	BCG A + A + A + A − T +
U. H.	10	BCG A + A + A + A + A − T +
K. J.	6	BCG A + A − T +
M. L.	6	BCG BCG A + A + A − T +
S. N.	13	BCG A + A + A + A − A − BCG A + A − T +
I. T.	6	BCG A + A + A − T +
U. B.	7	BCG A + A + A + A − T +
K. E.	11	BCG A + A − A − BCG A − A − T +
K. L.	10	BCG A + A + A + A + A + A + A − T +
L. S.	13	BCG A − A − BCG A + A − A − T +
K. J.	20	BCG BCG BCG BCG A + A − A − A − A − A − A − BCG A + A − A − A − T +
M. L.	7	BCG? A + A + A − T −
K. H.	16	BCG A + A + A + A − A − BCG A + A + A − T +
I. S.	6	BCG A + A − T −
I. G.	14	BCG BCG A + A + A + A + A − A − T +
K. S.	6	BCG A + A + A − T +
D. P.	5	BCG BCG A + A − T +
E. M.	12	BCG A − BCG A + A + A + A − T +
K. M.	8	BCG BCG A + A + A + A − T +
K. S.	11	BCG A + A − A + A − T +
M. N.	13	BCG A + A + A + A + A + A + A − T +
L. C.	18	BCG? A − A − A − A − BCG A + A − A + A − T −
M. R.	10	BCG A + A − BCG A + A − T −
A. L.	9	BCG A + A + A − A − A − T − BCG A − T − A − T −
U. S.	8	BCG A + A + A − T −
A. S.	6	BCG A + A + A − T −

TABLE 2

Thirteen student nurses negative to 0.1 mg of tuberculin on the arm, tested with the same dose on the left thigh. Symbols as in Table 1.

Case	No. tuberculin tests	BCG vacc. and tuberculin tests (in chronol. order)
M. L.	14	BCG A− A− A− BCG A+ A− A− A− T+
I. H.	16	BCG A− A− BCG A− A− A− A− A− A− T+
G. S.	12	BCG? A− BCG A− A+ A− A− T+
K. F.	9	BCG A+ A+ A+ A+ A− T+
B. L.	19	BCG A− A− A− A− A− A− A− A− T+
I. O.	11	BCG A− A− A+ A− A− T+
L. O.	8	BCG A+ A+ A+ A− A− T+
I. A.	17	BCG BCG BCG A− A− A− BCG A+ A− A− T+
H. Ö.	10	BCG A+ A+ A+ A+ A+ A+ A+ A− T+
B. E.	11	BCG A− A− A− BCG A+ A+ A− T+
I. S.	13	BCG A− BCG A− A− BCG A+ A− A− T+
I. N.	7	BCG? A+ A+ A+ A+ A− T+
U. E.	14	BCG A− A− A+ A− A− A− T+

From Table 1 it is seen that of the 39 "arm-negative" individuals, 26 ($\frac{2}{3}$) were positive on the thigh. In $\frac{2}{3}$ of the "thigh-positive" cases the test had been preceded by only one negative arm-reaction, but up to 4 negative arm reactions had previously occurred in one case (K. E.).

Experiment II.—This group comprised 13 student nurses, all negative to 0.1 mg of tuberculin on one of the arms. The average period of observation was 3 years, and the average number of previous tests during this time 12. The reactions are designated as in Experiment I. At the time the negative arm-reaction was read, or after a further 1–2 days, 0.1 mg of tuberculin was injected in the lateral surface of the left thigh, and this reaction was read after a further 72 hours. The results are shown in Table 2.

It is evident from Table 2 that all members of this group were tuberculin-positive on the thigh. In most cases the positive thigh-reaction had been preceded by one or two negative arm-reactions. In two cases (B. L. and I. H.), 8 negative arm-reactions had previously been recorded.

Experiment III.—Earlier workers (see above) have shown that the tuberculin reaction at a used site appears more rapidly than one at a new site. The reaction on the arm might therefore be expected to have passed by the time it was read, 72 hours after injection. For this reason the size of the reaction was measured after 6, 24, 48, and 72 hours. In order to establish the degree of any non-specific reaction (cutaneous reaction to the diluent),

control tests were carried out at the same time as the actual tests, a corresponding quantity of diluent being injected intracutaneously.

In Experiments I and II the tuberculin test on the thigh was performed as soon as 3–5 days after the injection on the arm. In experiments on rabbits Sandage and Birkeland have shown that tuberculin present in the body may increase a subsequent reaction. It is conceivable that, in the experiments now reported, the reaction on the thigh might have been influenced by the tuberculin injected a few days earlier in the arm. In order to form an estimate of this source of error, in Experiment III tuberculin testing with 0.1 mg on the left arm was therefore performed simultaneously with testing with 0.1 mg on the thigh. According to Leczinsky the reactions on the arm and thigh are identical.

Thirty-four student nurses (observation period 2 years, previous tests 6) were tested on the right arm ("used site") with 0.1 mg tuberculin and with the same volume of diluent on the left arm. Twenty-two of the subjects were negative after 72 hours, and these were retested on the 5th day after injection on the arm, with 0.1 mg of tuberculin on the right thigh ("new site"), with the same quantity of diluent on the left thigh, and with 0.1 mg of tuberculin on the left arm ("used site, repeated").

Of the 22 nurses who reacted negatively after 72 hours to 0.1 mg at the "used site", 9 were positive at the "new site". Of these 9, two were also positive on the left thigh. It should be noted that these were the only non-specific thigh-reactions, and that no non-specific reactions were found on the arms at 72 hours. Of the remaining 7 that were positive at the "new site", two were also positive at the "used site, repeated", but in both these cases the reaction was less marked than that at the "new site".

The tuberculin reaction at the "used site" was never as great as that at the "new site" (see Fig. 1). Our results differ in this respect from those of Weiss and Edwards & Magnus who, during the first 24 hours, noted a stronger reaction at the "used site" than at the "new site". In their experiments the "used site" had only been used once before, whereas in ours it had been employed for tuberculin testing on a number of occasions over a period of several years. Other differences, too, exist between the experiments. The chances of the "used site" tests, which were judged to be negative after 72 hours in experiments I and II, being judged as positive at 24 or 48 hours are very small (see Fig. 1).

The results of Experiment III also show that tuberculin present in the body may influence a subsequent tuberculin test. The reaction at 24–48 hours was less marked at the "used site" than at the "used site, repeated" ($0.02 > P > 0.01$, 48 hours; and $0.05 > P > 0.02$, 24 hours). It is less probable that this difference is due to the injection 5 days previously at the "used site, repeated". Thus in Experiment III the test at the "used site, repeated",

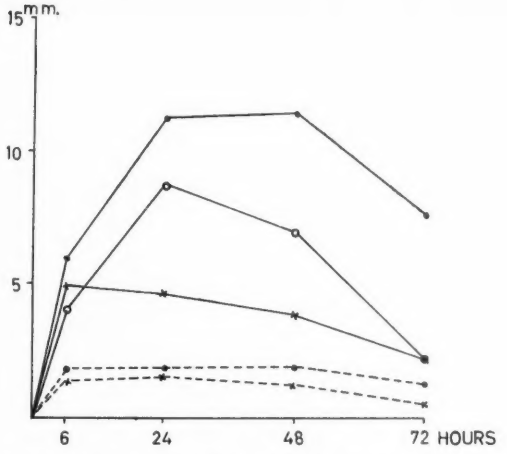

Fig. 1. Mean diameter of the infiltrate at different times.

×————× "Used site".
×– – – –× Left arm, diluent.
●————● "New site".
●– – – –● Left thigh, diluent.
○————○ "Used site, repeated".

is most suited for comparison with that at the "new site". At 72 hours the difference is statistically significant ($0.01 > P > 0.001$). The more rapid fading of the reaction at the "used site, repeated", is well illustrated by the fact that the later the reactions are read the greater is the difference between them. (See Table 3.)

The Experiments Compared

In Experiment I two-thirds of the subjects were positive on the thigh, in Experiment II all were positive at that site, and in Experiment III only 9 of 22 were positive on the thigh. The differences are explained by differ-

TABLE 3

The differences between the sizes of the areas of infiltration at the "new site" and the "used site, repeated", and their mean errors, after different intervals of time.

	6 hours	24 hours	48 hours	72 hours
$D \pm \varepsilon_D$	2.0 ± 1.5	2.5 ± 1.8	4.5 ± 2.2	5.4 ± 1.9
D/ε_D	1.31	1.38	2.05	2.87

ences in the composition of the groups. In Experiment I the subjects were selected on the basis of the stricter condition of a negative arm-reaction to 1 mg of tuberculin; those in Experiments II and III were only required to react negatively to 0.1 mg of tuberculin. Experiments II and III were similar in this respect, but differed in others. Thus the average observation period in Experiment II was 3 years, and the number of previous arm-tests 12; in Experiment III the period of observation was 2 years, and the number of previous tests during this time 6. The three experiments are therefore not comparable.

Conclusions

Many persons who have been strongly tuberculin-positive following BCG vaccination become tuberculin-negative after a time and remain so despite repeated BCG vaccination. The question is examined whether the disappearance of the tuberculin allergy is a general phenomenon in all cases, or whether it may be a purely local one associated with frequent tuberculin tests routinely performed on the arm. A total of 74 student nurses, previously tested 10–20 times on the arm and at the time of the experiment negative at that site to 0.1 or 1.0 mg of tuberculin, were retested on the thigh after 3–5 days with the same quantity of tuberculin. In 48 of the 74 subjects the thigh-reaction was positive at 72 hours. The stronger reaction on the thigh is only to some extent dependent on the tuberculin still present in the body following the first tuberculin test. The attenuation of the tuberculin allergy after repeated testing must therefore be regarded as a partly local phenomenon.

The local inhibition of the tuberculin reaction has not been considered in several investigations on that subject, and the phenomenon has been ignored in previous discussions on the nature of the delayed type of allergy.

Summary

Student nurses previously tested with tuberculin on the arms 10–20 times, and showing a negative reaction at that site, were in 48 out of 74 cases positive to the same quantity of tuberculin injected into the skin of the thigh. The negative reaction to tuberculin on the arms must therefore be regarded as a partly local phenomenon.

Inhibition locale de la réaction à la tuberculine après examens répétés de sujets vaccinés au B.C.G.

Des élèves-infirmières examinées à la tuberculine 10–20 fois au niveau des bras et ayant eu une réaction négative à ce moment, présentèrent dans 48 des 74 cas une réaction positive, lorsque la même dose de tuberculine était injectée au niveau de la cuisse. La réaction négative à la tuberculine au niveau du bras doit donc être considérée comme un phénomène partiellement local.

Lokale Tuberkulin-Unempfindlichkeit bei wiederholten Untersuchungen BCG-Vakzinierter.

Schwesternschülerinnen, die nach 10–20 Tuberkulinproben am Arm eine negative Reaktion an dieser Stelle aufwiesen, zeigten in 48 von 74 Fällen eine positive Reaktion, wenn die gleiche Dosis Tuberkulin in den Oberschenkel injiziert wurde. Die negative Reaktion am Arm muss somit als ein teilweise lokales Phänomen betrachtet werden.

Reacción negativa a la tuberculina, después de repetidas pruebas, en personas vacunadas con B.C.G.

Algunas enfermeras sometidas 10–20 veces a la prueba de la tuberculina en el brazo, con resultado negativo en cada caso, tuvieron una reacción positiva en 48 de los 74 casos al inyectarles la misma dosis de tuberculina en el muslo. La reacción negativa a la tuberculina en el brazo debe considerarse, por consiguiente, como un fenómeno parcialmente local.

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From the Department of Pediatrics, Rigshospitalet, University of Copenhagen, Denmark (Chief: Professor Preben Plum, M.D.)

Osteogenesis Imperfecta Associated with Ehlers-Danlos Syndrome: Addendum

A New Syndrome

by AXEL BIERING and TORBEN IVERSEN

In our report of a case of osteogenesis imperfecta associated with Ehlers-Danlos syndrome in a 1-year-old boy (*Acta Pædiat., 44:* 279–286, 1955) we concluded that the case might be interpreted as a particularly profound mesodermal malformation.

After the publication of our paper we have received a reprint of a Russian paper ("On Fibrodysplasia" by M. F. Maretskaja & L. A. Isajeva, *Pediatrija* (Moscow), *1:* 51–56, 1951) which deals with the same subject. The paper contains three case records, two of which are completely analogous to our case. This makes it unquestionable that the coexistence of the two conditions is not due to chance, but that we are confronted with a new syndrome.

As the paper is in Russian and has no summary in another language, a summary of two of the Russian case reports is given below.

Case 2.—A girl, 10 years old. Since the age of three years she had had eleven spontaneous fractures. Roentgen examination showed osteoporosis and a thin corticalis. There was extreme hypermobility of the joints. The subcutaneous tissue was poorly developed, and the skin on the abdomen could be picked up in folds 5–6 cm high.

Case 3.—A girl, 23 months old. She had sustained five fractures before the age of 7 months. Roentgen examination showed marked osteoporosis and an extremely thin corticalis. The skull was dolicocephalic. There was a marked hyperextensibility of the joints. The skin was thin, pale and dry and could be picked up in folds 6–7 cm high.

There were no known cases of similar malformations in the familes. The intelligence of the children was normal. The concentrations of calcium and phosphorus in serum were normal. Histological examination of the skin was not mentioned.

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SUMMARY OF SUPPLEMENTS

Adynamia Episodica Hereditaria

by INGRID GAMSTORP

(Summary of Supplement 108)

A disease characterised mainly by attacks of spontaneously abating paralysis, particularly of the muscles of the extremities and the trunk, is described under the name of adynamia episodica hereditaria. One hundred and thirty-eight patients with the disease are known. Sixty-eight were examined by the author. Of these, 17 were examined in hospital, where they were observed both between and during attacks, and where various methods of preventing, precipitating and controlling the attacks were tried.

The disease was found to be hereditary. The inheritance is due to a single, autosomal, dominant gene with complete or almost complete penetrance.

In more than 90 per cent of the patients the onset occurred below the age of 10 years, and only in 1 above the age of 30. The attacks occurred during rest after exertion in all patients. In about three fourths of the patients the attacks occurred at least once a week, and in roughly the same number the attacks lasted at most 1 hour. The extent and severity of the paresis varied from slight weakness of a single extremity to severe states in which the patient, when lying, was unable to turn over or sit up without help. The respiratory muscles were seldom involved, and when, only slightly. Mild symptoms from the musculature innervated by the cranial nerves had occurred at least once in about half of the patients. Gentle exercise at the appearance of the first symptoms of an attack or as soon as possible during an attack always gave relief. The intake of food, especially of bread, at the onset or during an attack warded off, or shortened the duration of the symptoms.

The disease was found to be equally common among males as among females, but the course was on the whole somewhat more severe in the males. During childhood the attacks were short and frequent, at puberty they became longer and more severe though not more frequent. The disease was usually most troublesome between puberty and about 30 years of age, after which improvement occurred in about half of the patients. Only 1 patient reported progression of the disease after 30 years of age. In a few of the patients the attacks ceased to occur after the age of 50–60. The disease was

more troublesome in cold, damp weather. The attacks were always more common during the day-time than at night. Working capacity was never more than slightly reduced. According to information from relatives, no patient has died from an attack of adynamia episodica hereditaria.

Only exceptionally did clinical examination, blood studies or electrocardiography between attacks reveal anything of interest. During attacks paralysis of varying extent and severity was observed, and in somewhat more than half of the attacks tendon reflexes were weak or absent. In somewhat less than half Chvostek's sign was positive. As a rule, the attacks were accompanied by an increase in the serum potassium without any decrease in the excretion of potassium in the urine and by such electrocardiographic changes as are seen in the presence of increasing serum potassium independently of the cause of the increase. Attacks could nearly always be precipitated by oral administration of a dose of potassium not large enough to produce symptoms in healthy persons. Calcium administered intravenously at the culmination of an attack usually soon controlled the symptoms. Glucose with or without insulin administered before, or simultaneously with, an otherwise provocative dose of potassium had a prophylactic effect, the attack then being prevented or less severe than otherwise.

Electromyographic changes occurred during an attack in the 4 patients studied: the innervation pattern changed suggesting loss of muscle fibres. In 3 spontaneous activity occurred or, if present, increased. In all 4 the mean action potential duration was significantly lower than before the attack. The treshold of motor response to the intra-arterial injection of acetylcholine was slow both between and during attacks.

The attacks abated spontaneously. Only in 2 patients, now aged 60, was permanent slight muscle weakness observed between attacks, and only in 1 was there any muscle atrophy, and then only slight. Histologic examination of a biopsy specimen of the muscle of the latter patient showed changes of the type seen in dystrophia myotonica. Histologic examination of muscle tissue from 2 younger patients without atrophy or permanent muscle weakness showed no evidence of a pathologic condition.

As yet, no effective treatment of the disease *per se* is available.

Acta Pædiatrica **45**: 659—670. Nov. 1956

The Danish Pædiatric Society

Meeting, January 28, 1956

in conjunction with the *Danish Society of Anaesthetists*, the *Gynaecological and Obstetric Society*, and the *Danish Neurological Society*.

The prophylaxis, treatment and sequelæ of asphyxia neonatorum.

SPEAKERS: Professor E. Brandstrup, O. Secher, P. W. Bræstrup and Professor M. Fog.

DISCUSSION: S. Brandt & V. Westergaard-Nielsen, D. Torup, A. Skov-Jensen, H. Moller, H. Buch, P. Plum, E. Christensen, F. Fuchs, B. Friis-Hansen, B. S. Pedersen.

To be published in *Nordisk Medicin*.

Meeting, February 29, 1956, in the University Paediatric Clinic.

Aagaard: **Demonstration (Coley's anaemia).**

J. Vesterdal: **Nephrosis following vaccination against poliomyelitis.**

The patient was a boy, aged 11 years, suffering from nephrosis which had developed following vaccination against poliomyelitis and was complicated by a subdural abscess. The boy complained of lassitude following the second vaccination and a week later he developed oedema. Nephrosis was revealed and was treated with A.C.T.H., cortisone and, simultaneously, with antibiotics. During this therapy, an abscess developed in the right eyelid and the boy developed seizures which proved to be due to a left subdural empyema. This was evacuated in the Department of Neurosurgery.

DISCUSSION.—*E. Gjorup:* Similar cases have been observed following combined diphtheria and tetanus vaccination.

Erna Christensen, J. Melchior and P. Plum: **Bilateral, symmetrical necrosis of the corpus striatum, formatio reticularis and spinal medulla in a boy aged 10 years.**

Published in *Acta pædiat., 45:* 396, 1956.

Folke Tudvad, J. Kringelbach and K. Biering-Sørensen: **B.C.G. vaccination of newly-born infants.**

In the Maternity Clinic, Martinsvej, Copenhagen, B.C.G. vaccination was offered to all newborn infants during the year 1950. Out of 2159 infants, the mothers of 1330

accepted the vaccination (61.3 per cent). Out of these 1330, information concerning the Moro reaction was obtained in 1199 (90.1 per cent) and among these there were 11 (0.9 per cent) who had not become Moro positive. By follow-up examination in the Maternity Clinic and review of the records kept by the Health Visitors is was found that 33 (2.75 per cent) had developed glandular abscesses following the vaccination.

From the records of weights kept by the Health Visitors of the infants in their homes, a calculation of the daily increase in weight was made for the first, second, third & fourth and fifth & sixth months of life of the infants who had been B.C.G.-vaccinated. Premature infants, infants in whom information concerning weight was incomplete, those suffering from serious illnesses as well as those where information concerning the tuberculin reaction was not available were excluded from the series. These weight calculations were compared with corresponding calculations for non-vaccinated infants with the same exclusions as above; infants who were B.C.G.-vaccinated later were also excluded. The calculations did not indicate that B.C.G. vaccination in the neonatal period influences the thriving of the infants in the first 6 months of life.

K. Biering-Sørensen, J. Guld, K. Magnus and K. Tolderlund: **Glandular complications of B.C.G. vaccination in the neonatal period with varying doses of vaccine.**

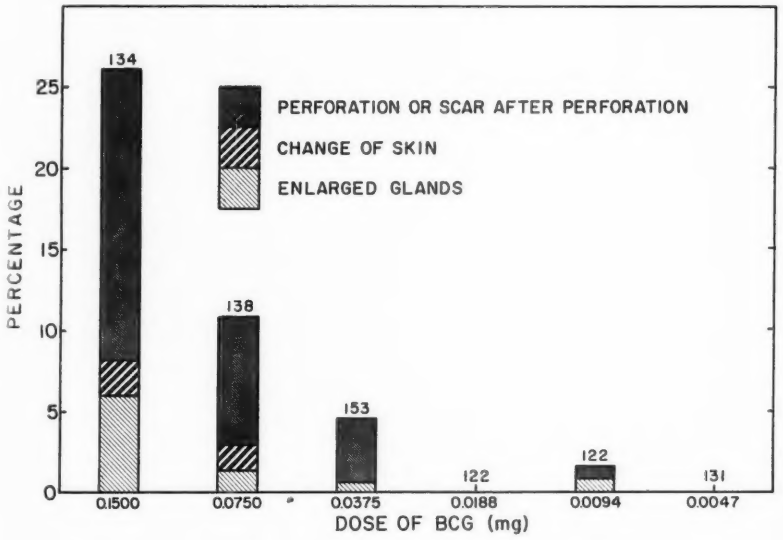
In November 1952, the results of certain investigations concerning the complications of B.C.G. vaccination in the neonatal period were submitted to the Danish Paediatric Society. Stimulated by these investigations, co-operation was established between WHO's Tuberculosis Research Office, the National Serum Institute, Copenhagen and the Municipal Organization of Health Visitors in Copenhagen. In the course of the past two years, systematic follow-up examination was undertaken throughout the entire first year of life of a group of children who were vaccinated immediately after birth with B.C.G. vaccines of varying strengths. The doses varied from 0.15 mg to 0.0047 mg administered either as one or two injections within the first 11 days of life. A total of 7 follow-up examinations of the children was performed in the first year of life in view of adenitis and other regional complications. Only glands which exceeded a certain size were included. The investigation comprized a total of approximately 1500 children.

In the preliminary account which comprises 800 infants vaccinated during the period November 1953 to August 1954 and followed up during the entire first year of life, a definite relation between the total amount of vaccine injected and the incidence of complications could be demonstrated. The result is recorded in Diagram 1.

It appears that adenitis was found in 25 per cent of the children following the injection of 0.15 mg vaccine, and in $\frac{2}{3}$ of these cases perforation of the glandular abscess occurred. With a dose of 0.075 mg vaccine, the incidence of adenitis was reduced to less than half and with a dose of 0.0375 mg, complications occurred only in 4 per cent of the children. If only perforation and skin changes over the adenitis (nearly always a sign of threatening perforation) be considered, the incidence of complications for the 3 most potent doses of the vaccine becomes: 20, 10, and 4 per cent. In the children vaccinated with the three weakest doses of vaccine, one case of glandular perforation occurred (approximately $\frac{1}{4}$ per cent).

The strength of the tuberculin reaction following Mantoux testing with 5 tuberculin units showed only a lesser diminishing on reduction of the dose of vaccine. Reduction

Frequency of enlarged and perforated glands among infants vaccinated November 1953 to August 1954 and followed-up for one year, according to total dose of BCG vaccine.



The number above each block indicates the number examined.

Diagram 1. The individual columns represent the percentage incidence of complications with a certain dose of vaccine. In order to simplify the diagram, this does not indicate whether the vaccine was administered as a single or as two injections. The dose falls according to a logarithmic scale from left to right so that the quantity of vaccine for a certain column is half of that in the column immediately preceding.

of the dose to $\frac{1}{4}$ of that employed at present implies an average diminishing of the infiltration on Mantoux testing of a couple of millimitres (to approximately 13 mm).

As a result of the present research, the strength of the vaccine in Denmark has been reduced from 0.75 mg to 0.375 mg per ml vaccine and it is recommended to administer a single injection of 0.1 ml only when vaccinating newly-born infants, i.e. $\frac{1}{4}$ of the dose hitherto employed.

A detailed account of these investigations was published in the *British Medical Journal* in October 1955. The final account of the entire material will be published at a later date.

Discussion.—*T. Kærn* stressed the difficult technique of intradermal vaccination and the striking fact that the number of complications occurring at the hands of inexperienced vaccinators did not exceed that of experienced vaccinators. Do tuberculosis physicians consider vaccination necessary?—*Henning Andersen* considered that complications were rarer following the scarification method. — *Groth-Petersen:* As regards the indications for vaccination, it is meaningless (too late) to vaccinate only when the environment is tuberculous. The occurrence of approximately 200 new cases of tuberculosis annually is probably sufficient indication for continued

vaccination, at any rate in the towns. — *Sigrid Holm* was definitely of the opinion that the technique of B.C.G. vaccination plays a role. This is obvious also from investigations undertaken by the Tuberculosis Research Office (TRO). In one of these investigations, B.C.G. vaccine was injected into 4 different layers of the skin, viz 3 injections at different depths intracutaneously and one subcutaneously. The deepest injections administered rendered a much greater number of local abscesses and abnormal scars. She would like to ask the team which worked with B.C.G. vaccination in the neonatal period if they were satisfied with the average allergy achieved? If, for example, the average allergy obtained on employing the standard vaccine (0.75 mg/ml) be considered, this appears to be somewhat lower than that found in children of school age with the same vaccine. — *J. Guld:* No evidence is available that the variation in the *degree* of immunity renders any difference of note in the protection against tuberculosis. — *P. Bræstrup:* Experience in the vaccination of school children in the County of Copenhagen shows that the increase in the incidence of complications results in a distinct fall in the number of vaccinations in the following year. — *J. Flamand-Christensen* raised the question of the most favourable period for B.C.G. vaccination in relation to other vaccinations: at the age of 10 months or *after* vaccination for smallpox at the age of 2 years. — *Tolderlund* accounted for the reduction of potency of the vaccine. — *Tudvad, in reply to Kærn:* Deliberately, no attempt was made to persuade mothers to let their infants be B.C.G.-vaccinated as an unvaccinated control group was expressly desired. As regards technique, Dr. Tudvad was definitely of the opinion that experienced vaccinators obtained fewer complications in the form of abscesses than did inexperienced vaccinators, and in his experience abscesses were the most unfortunate complications as they render vaccination unpopular. The presence of more or less pronounced glandular swellings is of no particular significance. Such swellings are not painful and do not demand special treatment. Dr. Tudvad would like to support Dr. Groth-Petersen's recommendation for B.C.G. vaccination in infancy. It is in infancy, in particular, that the danger of the serious complications is present. The most practical thing would probably be to perform the B.C.G. vaccination at the Health Examination at the age of 5 weeks as the examination at the age of 5 months is already taken up by combined diphtheria–tetanus immunization and that at the age of 10 months by vaccination against poliomyelitis. He considered it to be important that B.C.G. vaccination should be carried out by a physician who is specially trained in the vaccination of infants.

Meeting, April 18, 1956

***A. Henriques:* Reports of two cases from practice.**

***H. Dyggve and Bodil Farup:* Psychological viewpoints and experience concerning nervous children and their parents. With illustrative examples.**

H. Dyggve: The speaker has been employed for several years as paediatrician in the University Clinic for Child Psychology. Tables were shown to illustrate the clientele of the Clinic. The investigation comprised 514 children from a four-year period (1951–55). The age distribution shows that the majority are children between the ages of 5–10 years. The sex distribution shows twice as many boys as girls. This is because boys are more aggressive while girls more frequently become subdued and this does not disturb the parents so much. Forty per cent of the children had dis-

urbances of behaviour as the main symptom. Thirty per cent were unsettled, restless r had tics, sleeping or eating problems. Twenty per cent suffered from enuresis, ncopresis or both. Six per cent had difficulties in speech. In five per cent of the hildren, organic brain lesions were demonstrated and these had, as a rule, been cquired at birth. Ten per cent were born prematurely and eight per cent suffered rom asphyxia pallida at birth. Serious mental disorder was present in one or more f the child's nearest relatives in fifteen per cent of the cases. In twentyfive per cent f the cases, the child did not live with both his biological parents. Five per cent of he children were adopted. Fourteen per cent were only children. In the families in hich there were more children, there was a great preponderance of the oldest child ompared with the youngest.

Originally, the speaker had been sceptical of the penetrating psychological theories hich are difficult to grasp. He began, however, gradually to believe in the majority f the basic theories and thoughts as he learnt them so to speak from the children, aturally under the direction of psychologists. The speaker pointed out that a certain exual interest and fear concerning the child's body must be regarded as an ordinary henomenon. The so-called Oedipus-fantasies and "fear of castration" are seen parti- ularly at the ages of 4–5 years. Such fantasies are vague and become suppressed in ormal children while fear in connection with aggressive and sexual impulses is, as a ule, pronounced in neurotic children and adults.

The speaker was of the opinion that the cause of the widespread scepticism with hich psychologists and child-psychiatrists are regarded is partly the difficulty in ccepting the theories if there is no opportunity of employing them in practice under xpert guidance; further, this scepticism is due to the widespread but erroneous con- eption that penetrating psychologists advocate completely free and uninhibited ctivity in the children.

The case histories of three of the patients treated psychotherapeutically by the speaker were referred to.

It was the speaker's impression that extremely sensible and conscientious work is being carried out in the University Clinic for Child Psychology and that the results are frequently surprisingly good. As the need for help is great, the establishment of one or more clinics would be desirable.

Bodil Farup: No report submitted.

Discussion.—*P. Plum:* The figures given for the reasons for which the children were referred to the Clinic correspond to those seen in all paediatric departments. In addition to the two possibilities mentioned by Dr. Farup—analysis and a friendly pat on the back—there is a third possibility, viz., solving the problems for the parents and general guidance of the parents, possibly before the child is treated. — *Sv. Heinild:* With due acknowledgement of the excellent research work carried out in clinics for child psychology it should be pointed out that the prolonged therapy in such clinics in certain cases may function as a deflecting manœuvre where one loses sight of the essentials. Intense exploration of the psychopathology of a child may now and again imply that one ignores the principal emotional and social conflicts frequently present in the home where the child requires treatment on account of behaviour disturbances of various kinds; or those conflicts may not be attributed sufficient importance. If a "Strindberg environment" is present in the home and if this cannot be altered, treatment of the child, in the speaker's opinion, will most frequently be illusory. — *E. Gjørup:* In practice, economical factors must be considered. What does it cost to achieve results? Guidance is a possibility which lies near at hand but it must be employed

with great caution as direct guidance may be harmful. — *A. Rothe-Meyer* inquired about the results of short-term therapy: (1) extended guidance, (2) short-term therapy, versus (3) penetrating psychotherapy. What is the significance of *contact* during analytical therapy? — *J. Egsgaard:* The great majority of patients in a psychiatric department are too severely affected to respond to treatment of the environment alone but demand direct personal therapy. — *P. Drucker, A. Henriques and K. Biering-Sørensen* inquired about the scope and justification of the interpretation of symbols. — *P. W. Bræstrup:* Guidance and treatment of the environment, respectively, in one way or another are the only possibilities which can be employed in practice by paediatric departments.

Meeting, May 16, 1956

Niels J. Schierbeck: **Morbidity among school children in the borough of Gentofte in August–September 1955 with special reference to bathing in The Sound.**

(To be published in *Sundhedsplejen* and, in an abbreviated form, in *Ugeskrift for Læger.*)

Fleming Quaade: **The influence of heredity and environment on the height of school children.**

(Published in *Acta pædiat., 45:* 523, 1956.)

Boesen, Ib: **Prophylactic iron theraphy in a day nursery.**

During the months September–March, ferric tartrate (for preference in a daily dose of 0.10 g) was administered to every alternate child. Each group comprised 16 children with similar age distribution; in the treated group, 13 children were under the age of one year compared with 12 among the untreated children. The haemoglobin levels in the treated group at the commencement and conclusion of the experiment were 88 and 91 per cent, respectively, as compared with 91 and 89 per cent, respectively, in the untreated group. On an average, 40 per cent in the treated group suffered from catarrhal conditions as compared with 41 per cent among the untreated during the experimental period. Twenty-one per cent of the infants in the treated group developed redness of the buttocks and 15 per cent dyspepsias as compared with 11 per cent and 5 per cent among the untreated infants. The incidence of red buttocks appeared to be independent of whether the dose of iron administered was 0.20, 0,10 or 0.05 g daily, but the incidence of dyspepsia diminished when the dosage was reduced. The infants received most of their food in the day nursery and thus must be regarded as adequately nourished both quantitatively and qualitatively.

Discussion: *Ane Madsen* mentioned the results of investigations concerning the prophylactic administration of supplementary iron to infants in Infant Welfare Centres. The haemoglobin percentage was significantly higher in infants who had received supplementary iron than in infants in the control group who had not received this supplement. — *C. Friderichsen* declared himself to be an ardent supporter of prophylactic administration of iron on account of the following two observations: When the large doses of iron were introduced in 1917, a definite increase in weight and improved appetite occurred in children even if their haemoglobin level and their weight were normal. The speaker interpreted this as a sort of catalytic action on the enzymes in the stomach and intestines. (*Ugeskr. for Læger,* No. 11, 1919). The other observation is that

children who are admitted to hospital in the winter months with high fever and acute respiratory infections, very frequently show haemoglobin levels of under 80 per cent. The speaker, therefore, was of the opinion that prophylactic administration of ferric iron is just as important as the prophylactic administration of vitamins A, C and D. Children with low haemoglobin levels are less resistant to severe infections. Red buttocks have only very rarely been observed with the doses employed by the speaker. — *E. Gjorup, P. Drucker:* Both these speakers, too, had years of experience of the favourable effects of administration of iron.

Section of Pædiatrics and School Hygiene of the Swedish Medical Society

Meeting, March 9, 1956

B. Vahlquist, S. Sjölin and L. Garby: **Chronic refractory hypochromic anaemia with disturbed haem-metabolism.**

(To be published in *British J. of Haematol.*)

B. Broman: **A proposal concerning routine testing for Rh-immunization during pregnancy.**

(Published in *Sv. Läkartidning.*)

R. Zetterström: **Simultaneous occurrence of congenital deformities, haemolytic anæmia, and thrombopænia.**

(To be published elsewhere.)

Th. Ehrenpreis and N. O. Ericsson: **Results of treatment in atresia of the oesophagus.**

Fifty-one cases of atresia of the oesophagus have been treated at the Department of Paediatric Surgery, Caroline Hospital, Stockholm, during the 4 years in which the Department has been in existence (February 1952 to February 1956). Four were not subjected to operation: Three died soon after admission, and one was a mongoloid defective for whom surgery was refused. Twenty-seven (59 %) of the 47 cases operated on survived. The coincidence of other deformities was high (about 30 %), and this of course affected the outcome to some extent. The commonest of these deformities were organic heart disease, mongolism, and duodenal and anal atresia.

The series is divided into two groups. In 4 cases in which the distal oesophageal segment was absent reconstruction of the antethoracic oesophagus was performed or attempted, and all died (one was very weak, and the other three had multiple deformities). The method has been abandoned. Oesophago-gastrostomy was performed in 4 cases, one of which survived (birth-weight 2300 g). Of 39 cases in which the distal oesophageal segment was present and primary anastomosis was performed 26 survived, i.e. 67 %. Fifteen of 17 patients operated on during 1955 have survived, i.e. 88 %.

The principles we have followed in the treatment of oesophageal atresia are as follows. One-stage operation by the transpleural route, a gastric fistula being induced for purposes of nutrition; no oesophaegeal sound; tracheotomy only when specifically

indicated (2 cases). The infant was then placed in an incubator under continuous supervision and with frequent aspiration, ordinary air being used in the incubator, and oxygen being administered only when necessary. Concerning the late results, 5 patients developed stricture, and all but one were cured by passing sounds. The remaining patient has still to undergo final treatment.

G. Carlström: **Is the virus of canine distemper pathogenic to man?**

The pathogenicity of the virus of canine distemper in man has long been the subject of discussion. A few years ago, Victor Cabasso, the American virologist, observed that human gamma globulin contained a substance that neutralizes the virus of canine distemper. Accordingly, it seemed likely that a human subject might be infected by the same virus or some other closely related one. In clinical quarters the problem was attacked by John Adams, who presented clinical and serologic evidence of a correlation between canine distemper and infections in the air passages in children. The problem seemed to justify further investigation.

In the present study, the virus of canine distemper was adapted to baby mouse, and is now in its 80th mouse-passage. A neutralization test was worked out to ascertain immunity to canine distemper by means of mouse-inoculation. Adults and children of different ages were examined with regard to the occurrence of a serum-antibody neutralizing canine distemper. All the adults, the children over 11 years of age, and most of the children aged 6–11 years disclosed immunity to canine distemper. In some children between 6 and 4 years of age antibodies were found, and in others not. Below the age of 4 the serum rarely contains any substance acting on the virus of canine distemper. Very recently Karzon has published similar investigations which have given largely similar results. The immunity curve for canine distemper resembles that of several virus diseases commonly affecting man. It has not yet been possible to correlate the appearance of distemper antibodies with disease in man. In all probability infection with the virus of canine distemper or a closely related virus usually runs a subclinical course in man. It still remains to be established whether clinical signs may be present. The investigations are to be continued, and will be concentrated mostly on children below the age of 4, i.e. the age-group in which immunity to canine distemper has not yet become general.

Meeting, April 13, 1956

I. Bjelkhagen and H. Gladnikoff: **Dissecting, calcified disk hernia in an 8-year-old child.**

A girl aged 8 complained of pain in the thoracic part of the spinal column with restricted motility 2 weeks after injury. X-ray examination disclosed a calcified nucleus pulposus in the intervertebral disk caudal to D 6, with posterior perforation through the annulus fibrosus, the calcified nucleus dissecting behind the vertebral body to D 7. The calcification disappeared within 7 months, and the symptoms subsided in 3 weeks. Twenty-one cases of disk-calcification in children have been reported previously, one showing disk prolapse. Two-thirds of the lesions produced an impression on the adjacent vertebral bodies. The calcifications occur in the cervical and thoracic parts of the spinal column and the upper lumbar region. No such calcifications have been reported below L 2. They have been seen in children of all ages. There is no difference in sex-distribution. A history of injury is given in only 3 of the 22 cases.

G. Hackzell and C. Lundmark: **Familial juvenile nephronophthisis. (Fanconi.)**

Case reports.

L. Kjellén and G. Sterner: **APC and RI-67-group virus.**

Cases from which APC virus was isolated are described. Type 2 occurred in two girls, who showed atypical pneumonia with negative cold-agglutination. During the period September–November 1955, 12 children from whom APC virus of Type 7 was isolated were treated at the Samariten Children's Hospital and the Hospital for Infectious Diseases. A complement-fixation test to the agent isolated disclosed a significant rise in the titre during the course of the illness in 9 of the children. In one case no such rise in titre could be demonstrated, and in two cases the serum was not examined. One of these two children was treated for scarlet fever, but gave a history of a catarrhal infection a fortnight earlier. A girl of 8 months showed atypical pneumonia with a significant increase in the antibody titre to APC virus, Type 7. A boy aged 10 years had a high temperature, headache, conjunctivitis, cervical lymphadenitis, and 8 mononuclear cells in an otherwise normal cerebrospinal fluid; his complement-fixation reaction showed no increase in the titre to poliomyelitis virus, whereas a significant increase was noted to APC virus. The remaining 9 children (aged 5–12 years) had a high, generally fluctuating temperature for 4–10 days, with the general condition remaining normal. All had pharyngitis; rhinitis, conjunctivitis, and cervical lymphadenitis were less frequent. APC virus of Type 3 was isolated in 5 cases. Four of these disclosed a disease picture similar to the one just described. The fifth child (a boy of 5 years) had atypical pneumonia with negative cold-agglutination and complement-fixation reaction 1/16 on the 13th day and 1/32 during convalescence. The possible etiological relationship between the virus in question and the disease pictures is discussed.

Discussion.—*J. Barr:* A preliminary report on approximately 20 cases of APC (Type 3) infection, mostly during treatment at the Hospital for Infectious Diseases, Örebro, Sweden.

B. Zetterberg: A report is made on an epidemio-virological investigation of an outbreak due to APC virus at Kumla and Frövi during the Summer of 1955. The investigation was carried out at the Epidemiological Department of the National Bacteriological Laboratory in collaboration with Drs. A. Svedmyr and L. Kjelldén of the Central Bacteriological Laboratory of the Municipal Hospitals, Stockholm. The epidemic involved about 120 cases, chiefly children aged 7–14 years. APC virus of Type 3 was isolated from faeces, conjunctival swabs, and sewage from the two towns. Usual symptoms were headache, fever, pharyngitis, conjunctivitis, and diarrhoea.

G. Tunevall, E. Törnquist and J. Wasserman: **A clinical-bacteriological review of respiratory infections treated at the Samariten Hospital for Children, Stockholm, during a period of one-and-a-half years.**

The results of culture of routine nasopharyngeal and pharyngeal swabs (the pharyngeal swabs examined only for β-haemolytic streptococci) in infections of the air passages are analysed. Cases given chemotherapy or antibiotics on any of the 5 days preceding the tests are excluded. Pharyngeal swabs were taken from 76 cases of acute tonsillitis and/or pharyngitis, and nasopharyngeal and pharyngeal swabs from 351 cases. In the former group 53 were negative. Seventeen of the 23 positive cultures were obtained from children of over 3 years of age. Among the 351 patients examined

more fully examination, 30 had β-haemolytic streptococci, 78 pneumococci, 43 *H. influenzae*, 45 *Staphylococcus aureus*, and 6 gram-negative bacilli. Seventy-five children showed 2 or more of the above-mentioned types of bacterium, and 74 a normal flora or no growth. β-haemolytic streptococci and *Staphylococcus aureus* are commoner in children of above 3 years of age. Pneumococci and *H. influenzae* reach their maxima in the lower age-groups, chiefly between 1 and 3 years of age. It emerges that there is no particularly marked correlation between the disease-picture including the sedimentation rate, the blood count, the temperature, and the type of infecting organism. This indicates that bacteriological culture diagnosis is highly important. The results of treatment are recorded by the period elapsing from the first day of treatment to recovery. Infection with *H. influenzae* differs from the others by its prolonged course despite the free use of tetracyclin whenever this organism was suspected or isolated.

H.-O. Mossberg, I. B. Johnsson and L. Lundqvist: **Behaviour disorders and school performance in under-age school-children in the Solna elementary schools.**

The frequency of behaviour disorders in under-age children in the elementary schools has been compared to the school performance in Classes 2 and 4, and to a corresponding control series. No significant difference was noted between the two series. The frequency of behaviour disorders was distinctly higher than in Gedda's Gothenburg investigation (1948), however, which was carried out in a similar manner. Nervous disorders were commoner among under-age girls than among the control girls. The physical development in the under-age children was slightly in advance of that of other children of the same age not attending school. The incidence of behaviour disorders was noticeably higher among the under-age children living under unsatisfactory social condition in social classes "1" and "3" than among the controls. The marks of the under-age children were only slightly higher than those of the controls. The marks of the under-age children improved more between Class 2 and Class 4 than did those of the controls. The marks showed that the demands for admission to school of under-age children with a "school maturity test" on a level with the best third of the children of normal age are justified, if it is required that the children are to keep up with the class and not be overtaxed by the work. If, however, it is desired that the under-age child be given a chance of continuing his education at a higher level, then the demands should be increased, and other factors considered, such as the child's social class, the home-conditions, and any nervous traits.

Meeting, June 2, 1956

Å. Gyllenswärd: **The circulation in funnel chest.**

Patients with funnel chest are quite often assumed to be suffering from some organic disease of the heart, owing to the occurrence of murmurs, some anomalous X-ray appearance of the heart with enlargement in the frontal plane, and impaired working capacity. Increasing recourse to surgery in cases of funnel chest in childhood is noted in Sweden, and other countries, since Ekström and Quist introduced a technique that inconveniences the patient relatively little. After operation the signs indicating cardiac defect either disappear or diminish. The different types of funnel chest are reviewed. It is stressed that subjects in whom the chest is extremely flat must be regarded as having the same anomaly even if the sternum is only slightly depressed.

The respiration and circulation were examined in seven patients aged 5–15 years, cardiac catheterization and angiocardiography being performed before and after operation. No surgical complications occurred. The distance between the vertebral column and sternum was increased from 3–7.5 cm to 7.5–11 cm. Four patients showed impaired capacity on the bicycle ergometer, but this was corrected by the operation. Six cases showed murmurs that disappeared in 3 and became less marked in the others. The electrocardiograms became normal in all cases. The maximum respiratory capacity increased, but the vital capacity remained unchanged, as a rule lying within normal limits. In two cases clearly increased pressures in the right side of the heart and in the left auricle became normal. Angiocardiography disclosed signs of pressure in the right ventricle and pulmonary trunk. These acquired a normal form after operation. This was particularly clear in the transverse tomogram.

Four further cases were examined. Operation was not undertaken in three, as no circulatory or respiratory impairment was present. The fourth case has not yet been followed up.

It has thus been shown that funnel chest may affect the circulation and respiration.

L. Wranne: **Hypoplastic anaemia treated with cortisone.**

(To be published elsewhere.)

A. Killander: **Subdural effusion as a sequel to purulent meningitis in children.**

Two cases are reported of subdural effusion following purulent meningitis. In one case the effusion consisted entirely of blood. The patient was a boy of 10 months who had previously suffered from pneumococcal meningitis. The diagnosis was confirmed by subdural puncture on the right side, insufflation of oxygen into the subdural cavity with subsequent X-ray examination, and carotid angiography on the affected side. The oxygen moved freely over the entire right cerebral hemisphere without crossing the mid-line. Angiography revealed a space about 2 cm wide between the brain and skull, and occupied by fluid. Repeated subdural puncture was performed, and the condition of the patient improved greatly. In three cases of subdural haemorrhage following meningitis (Smith, H. D., *Advances in Pediatrics, 8:* 165, 1956) the original infection was due to meningococci. The case described above is therefore probably the first to be reported where the primary infection was due to pneumococci.

The second patient, a girl of 5 months, had a bilateral serous effusion after meningococcal meningitis. Sub-dural puncture performed at intervals of 2–3 days gave large yields (total 300 ml). The previously pronounced spasticity disappeared entirely. As in the former case, it was found after insufflation of oxygen into the subdural cavity that the gas was freely mobile over both hemispheres without any communication with the opposite side.

Comparison between the electrolytic patterns, protein-electrophoresis, and sugar contents of the serum and subdural fluid showed that the subdural fluid contained the same concentration of electrolytes but less glucose and protein. The protein pattern was identical in both, which suggests that the protein components of the subdural fluid are directly derived from the serum. This is in contrast to most previous reports. Finally, the indications for subdural puncture and neurosurgical exploration of the

subdural cavity are discussed. The immediate improvement after subdural puncture is apparent in cases with post-meningitic effusion, but the ultimate effect of this procedure on the prognosis has not yet been established.

M. Michaëlsson and S. Sjölin: **Anæmia in cirrhosis of the liver.**

(To be published elsewhere.)

B. Hagberg: **Disturbances in dental development in endocrine disorders.**

A short survey, with special emphasis on the changes found in hypo- and hyperparathyroidism and in hypothyroidism. Disturbances in dental development in non-endocrine disorders, such as osteopetrosis, cleidocranial dysostosis, and mongolism, are mentioned.

R. Berfenstam and K.-E. Fichtelius: **Local inhibition of tuberculin reaction after repeated testing.**

(To be published in *Acta Pædiat.*)

Acta Pædiatrica **45**: 671—674. Nov. 1956

BOOK REVIEWS

Handbook of Poisons. **Robert H. Dreisbach.**

Lange Medical Publications. Los Altos, Calif., U.S.A., 1955. 426 pages, richly illustrated. Price $ 3.00.

The author of this book is professor of pharmacology at Stanford University Medical School in San Francisco. The purpose of the book is, according to the author's preface, to provide a concise summary of the diagnosis and treatment of clinically important poisons. This purpose is fulfilled in an excellent way. In brief and clear wording, almost in telegraphese, clinical findings, treatment, prophylaxis and prognosis of common poisonings are described in a manner that will be a great help to practitioners and doctors at out-patient clinics. The handy book of pocket-book size is divided into 6 sections. The first contains general considerations of poisons and poisoning with suggestions regarding emergency management and general principles in the treatment of poisoning. The following sections deal with pesticides and other agricultural poisons, industrial hazards, household chemicals and food poisoning, medical poisons and plant and animal hazards. In an appendix various types of equipment for mechanical resuscitation available in U.S.A. are described. A satisfactory index assists the reader in finding a reference to the subject he is looking for. The writer knows of no other book of comparable scope and it will without doubt fill an important gap. We have to envisage new editions in rapid sequence because of the speed in which new drugs and household poisons are brought on the market.

Les explorations biologiques en pédiatrie. **Claude Polonowski and Jean Colin.**

Expansion Scientifique Française. Paris, 1955. 500 pages.

The increased importance of clinical chemistry and physiology in understanding of various diseases and their adequate treatment has also increased the need of easy readable text-books about these subjects. In order to fulfil this objectives such books should not only contain a detailed description of common methods but also an account of the special findings characteristic of various pathological conditions. In this work there are two principal parts. In the first, a careful report is given of available chemical methods of examination. Various micromethods have been described at some length. The second part of the book deals with subjects such as electrolyte metabolism, acid-base balance, calcium and phosphate metabolism and the function of the liver and kidney. In special chapters endocrinology, blood-clotting and diagnosis of hemolytic diseases are discussed in a concise manner and with didactic skill. The recommmended methods of analysis have been chosen carefully and techniques that are too complicated have been avoided. The references are rather complete, but partly unsatisfactorily listed: in some cases only one author is mentioned and his co-workers omitted and it is sometimes difficult to use the references because the shortenings do not always comply with those recommended by the *Quarterly Cumulative Index Medicus*. The book, which is the first one in its type published in French language, gives

a good survey of the enormous importance clinical chemistry has gained in modern pediatrics. It fills a great need and can be recommended warmly, especially to be studied in pediatric biochemical laboratories.

R. Zetterström

Examen neurologique du nourrisson. **André Thomas, Yves Chesni and Mme St.-Anne Dargassies.**

La Vie Médicale. Paris, 1956. 47 pages. Price 450 Fr.

This booklet is written by a group of child-neurologists who work in Paris under the leadership of André Thomas (the latter has previously published several articles and books on the neurology of the newborn and the infant). The present work is divided into two parts. The first treats the newborn period. The authors give a detailed description of history-taking and the examination of the newborn infant with suspected intracranial injuries. A refined technique of examination is described, illustrated by numerous figures. The second part of the book treats the period of infancy from birth to the end of the first year. The normal development of the infant and the methods of assessment of motor development, muscle tone, reflex-activity etc. are reported. By means of the recommended technique it would be possible to determine if there are any lesions of the central nervous system and to treat children with such injuries at an early stage. The booklet can be recommended to pediatricians who are especially working with children with cerebral palsy.

M. d'Avignon

Die genuine Vitamin-D resistente Rachitis. **Walter Swoboda.**

Verlag für medizinische Wissenschaften. Wien, 1955. 80 pages with 12 figures and 5 tables. Price DM 10.

The primary D-vitamin resistant rickets has now been clearly differentiated from other types of D-vitamin resistant rickets. The etiology and pathogenesis are unknown but there is probably a dominant genetic trait. The author of this book has observed no less than 11 cases in only 2 years at the Pediatric University Clinic of Vienna. After a survey of the clinical signs and symptoms and the roentgenologic, histologic and biochemical characteristics of the disease, the author reports his own studies. He has shown that high doses of intravenously administered D-vitamin with simultaneous phosphate infusion provokes a temporarily increased tubular reabsorption of phosphate, which he considers due to an inhibition of the function of the parathyroid. These studies cannot give sufficient support to the theory that the nature of the disease is a primary tubular defect producing a deficient phosphate reabsorption. The author also gives a report on some attempts to demonstrate a deficient intracellular phosphate metabolism of the red blood corpuscles by means of radioactive phosphate. These studies are still in a preliminary stage and cannot permit a definite evaluation. The author seems to be of the opinion that the etiology of the disease is an enzymatically dependent deficiency of the phosphate metabolism. This study is too preliminary to give a clue to the solution of the problem of the etiology of the primary D-vitamin resistant rickets. The book gives, however, an excellent review of these problems and of the clinic and treatment of the disease.

J. Winberg

Pediatric X-Ray Diagnosis. John Caffey.

Year Book Publishers. Chicago, Ill., 1956. 3rd edition. 1059 pages, richly illustrated. Price $ 28.00.

More detailed comments on the 3rd edition of this well-known book seem superfluous as it is universally appreciated as an outstanding standard work lacking real competition. It is an excellent book from a medical as well as from a typographical point of view. Reading this book is a true enjoyment. It can be warmly recommended.

S. R. Kjellberg

My Left Foot. Christy Brown.

Secker A Warburg. London, 1954.

This is a very charming book that can be recommended and should be read by physicians and laymen alike. It is an auto-biography of a young man suffering from extrapyramidal cerebral palsy due to trauma at parturition. It is written in a touching way, and in simple words, by an intelligent adolescent who, having almost unsurmountable speech difficulties and paralytic hands and arms, taught himself to use the only part of his body that was somewhat spared, the left foot, in order to contact his personal environment. It is very enlightening to see cerebral palsy from within, to experience how these children feel, think and react, and it is encouraging to find how far it is possible to overcome difficulties by indefatigable patience, by faith and hopeful energy. It is difficult to tell which of the persons acting in the book one will bestow the highest admiration, the invalid, his mother or his helper in need, the well-known Dublin pediatrician Robert Collis. The latter, who is a renowned fiction author, has written a foreword in which he tells how he turned out to be Christy Brown's physician, teacher and friend. It is seldom that I have read a book so rapidly, provoking a mixture of smiles and tears. The last chapter in which Christy Brown and Robert Collis are the principal actors at a philanthropic concert is a jewel of psychologic wisdom. Every doctor who works with cerebral palsy children, and every parent who has children of his own suffering from this disease, should buy and read this book. It will give them satisfaction and hope.

Untersuchungen zur Nebennierenrindenfunktion im Säuglingsalter. H. Zeisel.

Karger, Basel/New York, 1956. 95 pages, 33 figures, 5 tables. Price Sw. Frs. 12.50.

This book is a review of the present knowledge of adrenal function in infancy and a report of the author's own work in this interesting field. The author has studied adrenal function in newborn, full term and premature babies and in older infants by conventional methods. Normal babies have been compared with infants with various diseases. Premature and full term babies excrete "corticoids" from the first day of life and in large amounts, if values are correlated to body surface or body weight. The excretion of 17-ketosteroids is larger during the first four weeks than during the rest of infancy. Infants react with an increased adrenal activity during situations of stress.

The methods employed have not been evaluated by the author and more recent methods as determination of 17-ketogenic steroids have not been used. In spite of these critical remarks the book is a valuable introduction into the problems of adrenal function during infancy.

C. G. Bergstrand

Urologie de l'enfance. **Gaston Lauret.**

Expansion Scientifique Française. Paris, 1956. 446 pages, 330 figures. Price 3900 francs

In collaboration with some French colleagues Lauret has published a text-book called "ce premier essai d'urologie de l'enfance". It deals only with the urinary tract the genitalia are excluded. Some parts of the book are good and so are the drawi illustrations. Other parts are not completely up to date. The value of roentgen exa mination is underestimated. The references are incomplete; some authors referred t in the text are not to be found in the references. Extremely bad reproductions o photographs and roentgenfilms.

N. O. Ericsson

Books Received

L'asystolie primitive chez l'enfant. Guy Lascombes. Imprimerie Berger-Levrault Nancy, 1956. 147 pages.

Stress. Fifth Annual Report. Hans Seley and Gunnar Heuser. Medical Encyclopedia Inc. New York, 1956. 815 pages.

Masked Epilepsy. Hugh R. E. Wallis. E. & S. Livingstone Ltd. Edinburgh and London, 1956. 51 pages. Price 7 s. net.

Undersuchungen zur Nebennierenrindenfunkion im Säuglingsalter. H. Zeisel. S. Karger. Basel, 1956. 95 pages, 33 figures, 5 tables. Sw. Frcs. 12.50.

Handbook of Poisons. Robert H. Dreisbach. Lange Medical Publications. Los Altos, Calif., 1955. 426 pages, numerous illustrations. Price $ 3.00.

Vergiftungen im Kindesalter. Prof. Dr. Herbert Brugsch. Ferdinand Enke Verlag. Stuttgart, 1956. 222 pages. Price DM 25.50.

Treatment of the Child in Emotional Conflict. Hyman S. Lippman. McGraw-Hill Publishing Company. London, 1956. 298 pages. Price 45/–($ 6.00).

Therapie mit ACTH, Cortison und Cortison-Derivaten bei Kinderkrankheiten. Dr. Fritz Souchon. Ferdinand Enke Verlag. Stuttgart, 1956. 109 pages. DM 21.—.

Acta Pædiatrica 45: 675. Nov. 1956

ANNOUNCEMENTS

Ninth International Congress on Rheumatic Diseases
Toronto, June 23–28, 1957

The Ninth International Congress on Rheumatic Diseases will be held at Toronto, Ontario, Canada, from June 23 to 28, 1957. This quadrennial function of La Ligue Internationale contre le Rhumatisme will be held under the auspices of the Canadian Rheumatism Association.

The Program Committee invites contributions to the scientific program of the Congress and is anxious to receive reports on current clinical or basic research dealing with any aspect of the rheumatic diseases.

Those offering papers for consideration should submit a 200- to 300-word abstract not later than the 1st of January, 1957. Abstracts should be submitted in triplicate in the language in which the paper is to be read. If an abstract is submitted in a language other than English, it will be helpful, though not essential, if it can be accompanied by an English translation.

All correspondence should be directed to:

The Ninth International Congress on Rheumatic Diseases
Post Office Box 237
Terminal "A"
Toronto, Ontario, Canada

The following *publications of the VIII International Congress of Pediatrics* in Copenhagen, Denmark, July 22—27, 1956, are available at the following prices:

Exhibition Catalogue, 130 pages (published July 1956), Dan. Crowns 15. –
Abstracts of Papers, 148 pages (published July 1956), Dan. Crowns 20. –
Discussions, about 176 pages (to be published in November 1956), Dan. Crowns 20. –
All three publications, Dan. Crowns 50. –

Active members of the Congress will receive the Discussions without cost.

Orders should be sent to Overlæge J. Vesterdal, Rigshospitalet, Børneafdelingen, Copenhagen Ø, Denmark.

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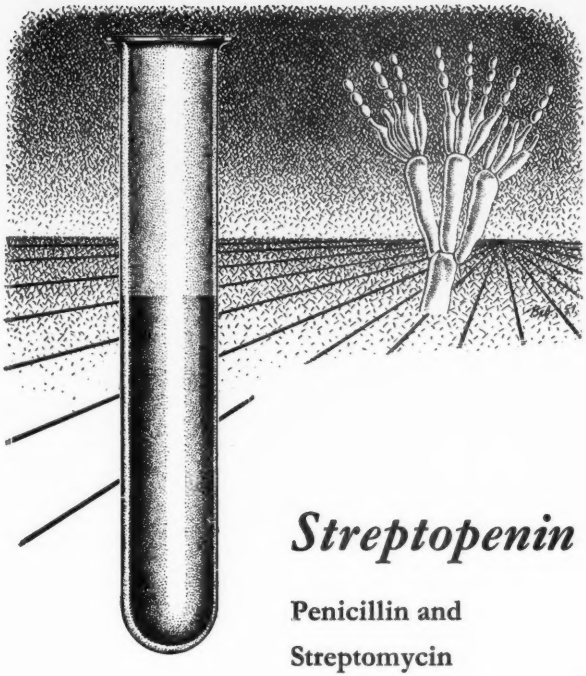

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6 — 10 år	1 sked × 4 — 5
11 — 15 år	2 skedar × 3 — 4
Vuxna	2 skedar × 4

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Findus har sedan 1948 tillverkat ett vällingpulver som tillredes med *färsk mjölk eller mjölkblandning*. Erfarenheten torde ha visat, att denna produkt, *Findus Välling*, är väl lämpad för barn från och med 4 månaders ålder.
Det har dock framkommit önskemål om att Findus skulle tillverka ett vällingpulver även innehållande torrmjölk och till vilket vid beredningen endast *vatten* behöver tillsättas. En dylik produkt skulle framför allt vara bra vid de tillfällen, då det är svårt för hushållen att skaffa färsk mjölk eller mjölk av god kvalitet, exempelvis under sommaren, på resor o.s.v. Med anledning härav har vi påbörjat tillverkningen av en dylik välling, kallad

Findus Välling med mjölk i pulverform.

Sammansättningen

Findus Välling med mjölk har utexperimenterats i samråd med vår medicinske konsult, och produkten har prövats noga under det senaste året. Sammansättningen har valts så, att den färdiga vällingen i stora drag motsvarar sammansättningen hos Findus Välling enligt receptet för barn i åldern 6—9 månader. Mjölet i båda produkterna utgöres av en blandning av vete, havre, råg och korn. En väsentlig skillnad mellan de båda produkterna är, att den nya vällingen innehåller vegetabiliskt fett, under det att Findus Välling innehåller animaliskt fett. Skälet är, att vegetabiliskt fett är betydligt hållbarare än animaliskt, när det torkas tillsammans med mjöl till ett pulver.

Kalorier	420	
Proteiner	20,6 g	
Kolhydrater	60,6 „	
Fett	8,9 „	
Kalcium	0,7 „	(1 g)
Fosfor	0,6 „	
Järn	8 mg	(7 mg)
Vitamin B_1	0,7 „	(0,6 „)
„ B_2	1,5 „	(0,9 „)
„ Niacin	5,2 „	(6 „)
„ C	25 „	(35 „)

En portion (ca 250 g) färdiglagad *Findus Välling med mjölk* har följande sammansättning: Kalorier 160, proteiner 7,8 g, kolhydrader 23,0 g, fett 3,4 g. Till 1 liter färdig välling åtgår 160 g vällingpulver.
Findus Välling med mjölk är berikad med vitaminerna B_1, B_2, niacin och C samt med mineralämnena kalcium, fosfor och järn. 100 g pulver har en sammansättning enligt tabellen ovan. (Siffrorna inom parentes anger dagsbehovet för barn upp till 3 år.)

Tillagning

Vällingen tillagas på så sätt, att 1 dl vällingpulver vispas ned i 2 dl vatten, varefter blandningen värmes under omrörning. Efter råd av vår bakteriologiske konsult ger vi numera på våra vällingpaket den anvisningen att *all välling åt barn under 1 års ålder bör ges ett snabbt uppkok*. För äldre barn och vuxna behöver vällingen endast värmas till lagom temperatur.

Bakteriologisk kontroll

Tillverkningen av välling sker under strikt hygieniska förhållanden. Hälsotillståndet hos all i denna tillverkning sysselsatt personal kontrolleras med jämna mellanrum av Findus läkare, dr Sven Ranklev. Bakteriologisk odling utföres sålunda varannan vecka å hals- och näsprov samt å faecesprov 2—3 gånger årligen. Dessutom utföres Widal-prov. Skärmbildsundersökning utföres en gång om året. Samtliga dessa prov utföres även på all personal som skall nyanställas på avdelningen.

Hygienen inom arbetslokalerna kontrolleras fortlöpande av Findus bakteriologiska laboratorium. Alla råvaror och färdiga produkter underkastas kontinuerlig bakteriologisk kontroll efter en plan som utarbetats i samråd med bolagets bakteriologiske konsult.

Pris och förpackning

Findus Välling med mjölk förpackas i värmeförsluten polyetenpåse och ett ytteremballage av papp och cellofan. Kapseln rymmer 400 g och kostar 2:35 (riktpris). Innehållet i en kapsel räcker till ca 2,5 l färdig välling.

För att skilja de bägge vällingpaketen åt har vi gjort en förändring av emballaget på Findus Välling. Den nya vällingen, *Findus Välling med mjölk*, packas således i *gul* kapsel, medan *Findus Välling* packas i *blå* kapsel. På kapseln för *Findus Välling med mjölk* är för ytterligare förtydligande också angivet att "endast vatten tillsättes".

Reklam

Barnläkarna önskar som bekant icke reklam för barnvälling i sådana former, att man genom denna riskerar, att mödrarna går ifrån modersmjölksuppfödning i onödan.

Findus har förklarat sig villigt att respektera detta önskemål. I konsekvens härmed kommer Findus nya välling med mjölk ICKE att annonseras i pressen för allmänheten. Däremot kommer vi naturligtvis att upplysa handeln om den nya produkten och lämna information om densamma till alla inom barnavården verksamma genom annonser i fackpressen. För information om den nya produkten är mödrarna således hänvisade till läkare resp. barnavårdscentraler.

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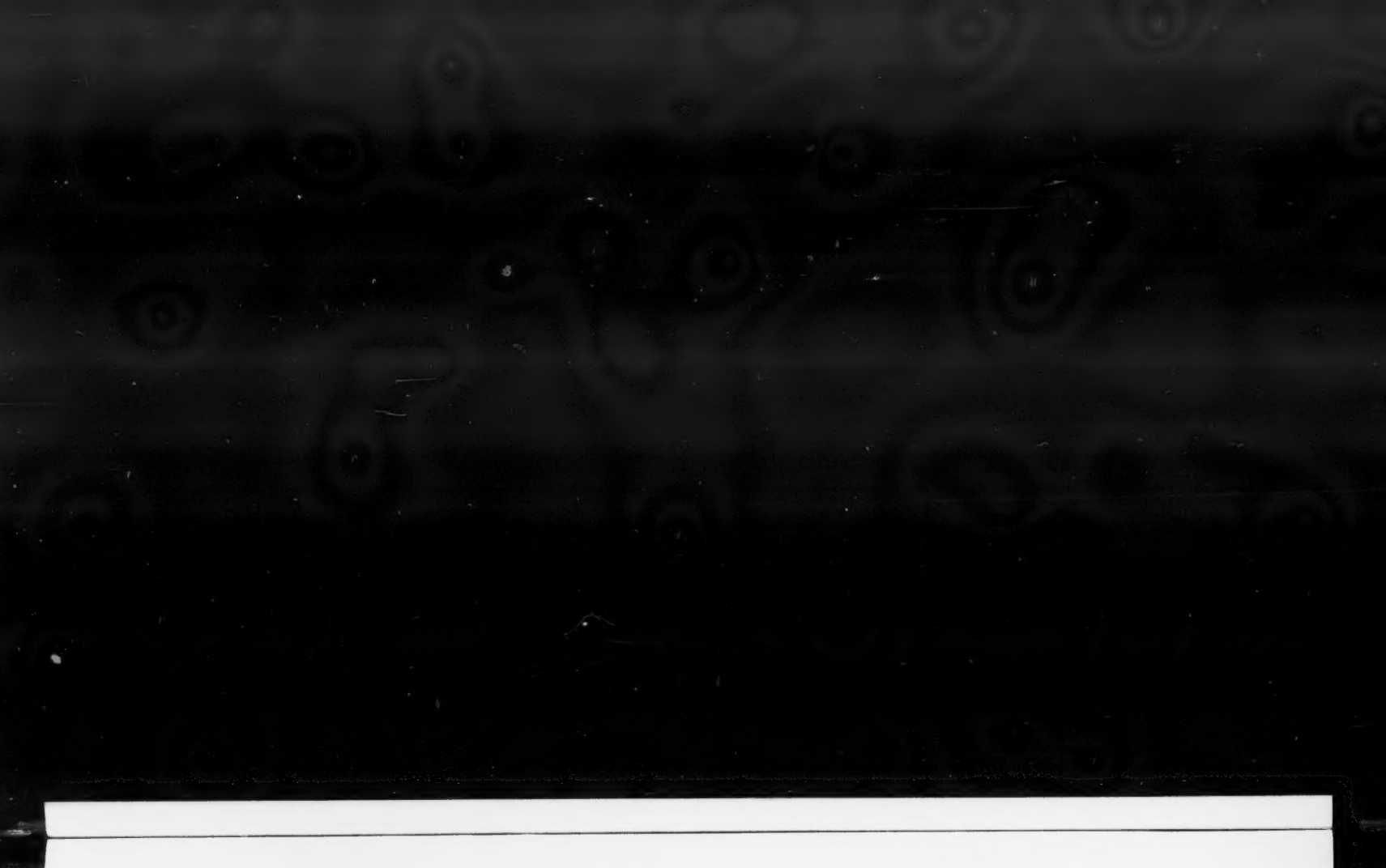
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